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American Journal of Obstetrics and Gynecology

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Original Communications

THE VALUE OF VAGINAL SMEARS IN THE DIAGNOSIS OF EARLY MALIGNANCY*†

A Preliminary Report

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ANY procedure that facilitates the early diagnosis of a disease as devastating as carcinoma of the uterus deserves serious consideration and extensive trial. In spite of improved therapeutic methods, clinicians are often handicapped by their inability to discover the neoplasm early enough to insure the maximum effect from the available therapeutic measures. Papanicolaou[1-3] and his associates, who have studied the cellular details of vaginal smears for a number of years, have opened a field that may eventually revolutionize the story of pelvic carcinoma in women. The material included in this survey is submitted as a preliminary report of the results obtained from the microscopic examination of the vaginal fluid aspirated as a routine procedure from a selected group of gynecologic patients. Papanicolaou does not claim that this method of diagnosis is the final answer to the problem, but the results obtained would seem to indicate that it is a step in the right direction. He further maintains that, "The vaginal smear should be considered as an accessory or preliminary method of diagnosis, and the actual demonstration of malignant cells in the biopsy specimen should be the basis for decision as to the method of therapy."[3] In the management of our cases, we too, have felt that patients whose vaginal

*This study was in part carried out by the generous contributions of Jeremiah Millbank, William Burton Jr., and Elise Strang L'Esperance.

†Presented at a meeting of the Section on Obstetrics and Gynecology of the New York Academy of Medicine, January 25, 1944.

smears were indicative of malignancy should be subjected to further study, and that the tissue sections must be the criterion for final diagnosis.

Method of Examination

The method of obtaining the vaginal smear is simple. The equipment necessary for each aspiration consists of a slightly curved glass pipette to which is attached a small rubber suction bulb; two microscopic slides, each equipped with a paper clip; and a fixative (a mixture of equal parts of 95 per cent ethyl alcohol and ether).

The smear is taken before any examining lubricant is used. The labia are separated and the pipette is introduced high into the vaginal vault, with the bulb compressed. As the pipette is withdrawn, the bulb is then slowly decompressed. The material thus obtained is then sprayed over the surface of the slide and spread evenly. Better cellular differentiation is effected when smears are even and thin. The moist slides are immediately immersed in the fixing solution where they may remain for an indefinite period. The vaginal spreads are stained either by Papanicolaou's method,[4] or by a modification of it developed at our laboratory at the Post-Graduate Hospital.[5] Both stains have the specific properties for emphasizing maximum nuclear detail, which is of paramount importance for accurate diagnosis, but the examiner's ability to recognize abnormal cells and interpret their histologic peculiarities requires a thorough knowledge of normal vaginal cytology. The diagnosis of malignancy is made from the vaginal smear just as it is from the tissue section, depending upon the presence of cells which exhibit structural abnormalities. In the smear, aberrant cellular forms are much more striking than in the section. Certain characteristic features are recognized as being common to vaginal smears from both cervical and fundal carcinoma. These are evident to the experienced investigator with low-power microscopic examination, and may be enumerated as follows:

1. Large numbers of leucocytes, chiefly polymorphonuclears, are commonly found. These tend to be clumped as well as scattered, and many are seen engulfed by other cells.
2. Bacteria are numerous.
3. Red blood cells are found in varying numbers even in the early stages. Generally, they will have lost their clear-cut outlines and appear crenated, degenerated or as shadow forms. The finding of red blood cells is considered so important, that in their absence, one should hesitate to render a positive diagnosis of malignancy. There are, however, exceptional instances of some very early cases in which red blood cells are not found.
4. The degree of cornification is frequently higher than in smears from nonmalignant cases, and it is common to find the cancer cells themselves cornified.
5. Histiocytes, appearing as single cells, are very common. They are large, foamy, often multinucleated cells, whose cytoplasm engulfs leucocytes, cellular debris and degenerated red blood cells.
6. Bizarre cellular forms are found of varied size and shape. The cytoplasm is hyperchromatic and contains deeply staining granules. Vacuoles are frequently found, and these often contain ingested cellular debris. The nuclei of these cells are dense, granular, irregular in form and may show prophases or arrested phases of mitosis. These are the malignant cells which determine the final diagnosis.

Clinical Investigation

This study includes the examination of 434 patients. Of this number, seven failed to return for proper follow-up; the conclusions, therefore, are based upon 427 cases. Two hundred and forty-five individuals were seen in the Strang Clinic, and one hundred and eighty-two in the Gynecological-Endocrine Clinic of the New York Post-Graduate Hospital. In 91 cases, a diagnosis of malignancy was made from the vaginal smears, of which 82 were confirmed by biopsy or curettage. The diagnosis of carcinoma of the cervix was made in 53 instances; carcinoma of the fundus in 37, and sarcoma of the cervix in 1 case. Of the slides examined at the Post-Graduate Hospital, 43 positive slide diagnoses of cancer were made; 31 of which were of carcinoma of the cervix; 12 cases of carcinoma of the fundus, and 1 of sarcoma of the cervix. Forty-eight positive smears were obtained from the Strang Clinic; 22 of which were indicative of cervical carcinoma, and 25 of carcinoma of the fundus. Confirmation of the vaginal smear diagnosis was obtained through tissue study in all but 9 instances. In 7 cases, a negative smear diagnosis was reported, which was subsequently proved incorrect when curettings were submitted.

The characteristic feature of a smear indicative of carcinoma of the cervix is the aberrant cell which may assume one of many forms. These cells present all the characteristics of a malignant cell and vary in outline. Variations include amoeboid, tadpole, saddlebag and other irregularly shaped cells. The presence of cells such as these, plus the diagnostic features already mentioned, indicates cervical malignancy.

Case 1.—Mrs. M. H., aged 58 years, was first seen in the Strang Clinic November 25, 1941, complaining of vaginal spotting of 4 months' duration and low abdominal pain. Her past history was irrelevant, and the menopause had occurred at 43 years. At her first clinic visit, vaginal smears and a cervical biopsy were taken.

Vaginal Smear Report: 11/25/41. (Fig. 1.) A large number of polymorphonuclear leucocytes is present and a moderate number of red blood cells. There are many deep cells characteristic of the menopause. In addition, there are numerous plaques of aberrant cells. These are irregular in shape and consist chiefly of tadpole forms. The cytoplasm is hyperchromatic and granular, and the nuclei are dense and contain abnormal granules of various sizes. The smear is consistent with squamous carcinoma of the cervix.

Pathological Report: 11/26/41. (Fig. 2.) A small piece of tissue is present, which is made up almost entirely of large, irregular squamous cells with deep staining nuclei, many of which contain mitotic figures. The stroma is markedly infiltrated with small lymphocytes and some polymorphonuclear leucocytes. The tumor cells are seen to be invading the stroma in several areas.

Diagnosis: Squamous carcinoma of the cervix—Grade II.

Management: The patient was referred to the x-ray department for therapy. Beginning November 26, 1941, she received a cycle of deep x-ray amounting to 2,450 r. to 4 pelvic portals. February 4, 1942, a radon bomb of 1,000 mc. hr. was applied. During this period of treat-

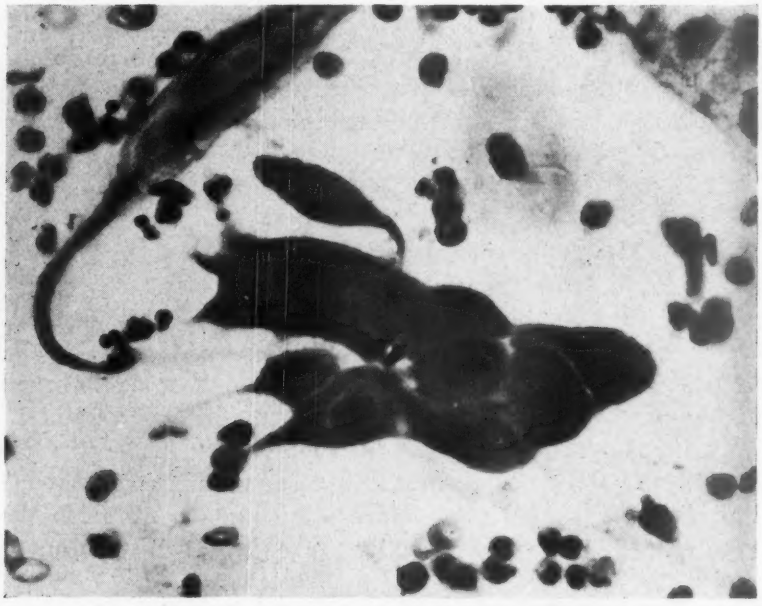

Fig. 1.—Carcinoma of cervix—vaginal smear. Magnification (×810).

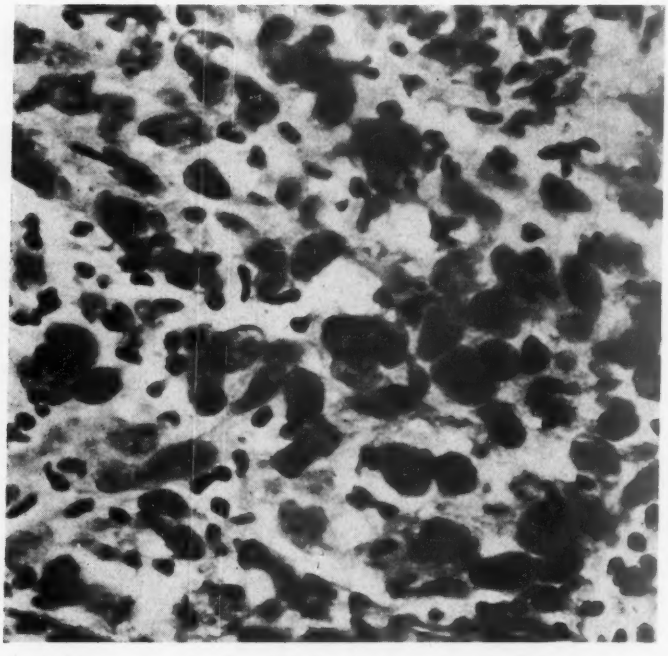

Fig. 2.—High power tissue—carcinoma of cervix. Magnification (×810).

ment, vaginal smears and cervical biopsies were taken. The first negative smear was obtained in October, 1942. Repeated vaginal smears taken in the follow-up clinic since then have all been negative. Her last clinic visit was December 14, 1942.

The diagnosis of carcinoma of the fundus is based upon the presence of malignant endometrial cells. There were 35 cases in which this diagnosis was made and confirmed. The cell upon which the diagnosis is based is small, round or cuboidal, slightly larger than a leucocyte. The nucleus is large in proportion to the size of the cell, stains deeply and is granular. Vacuoles are a common finding and may be so large and prominent as to displace the nucleus to the periphery, causing the cell to assume a signet-ring appearance.

CASE 2.—Mrs. M. S., aged 56 years, was first seen in the Strang Clinic April 25, 1942, complaining of vaginal bleeding of six weeks' duration. Her menopause had occurred at the age of 47, and was uneventful. Her past history was not significant. She was admitted to the hospital with the diagnosis of uterine fibromyoma April 26, 1942. The following day, a total hysterectomy was performed for degenerating submucous fibroid.

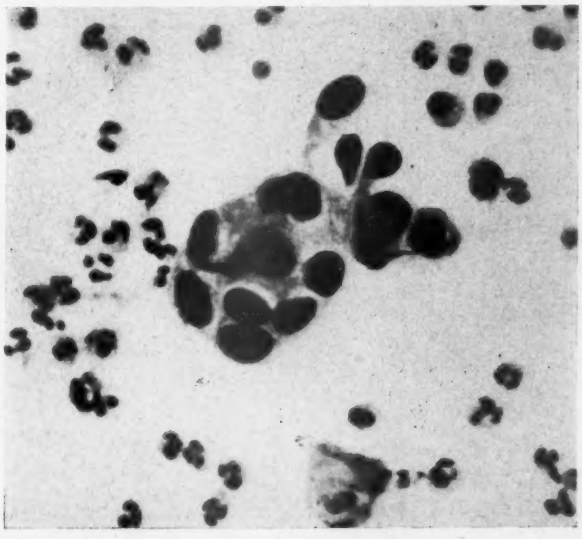

Fig. 3.—Adenocarcinoma of fundus—vaginal smear. Magnification (×810).

Vaginal Smear Report: 4/25/42. (Fig. 3.) A large number of polymorphonuclear leucocytes is present in addition to a large number of red blood cells. The slide is deep menopausal in type, and malignant cells are seen. These cells consist of clumps of small round cells with large, dense, irregular nuclei. Many are vacuolated and are of the signet-ring type. There are a few amoeboid and tadpole forms. The smear is consistent with adenocarcinoma of the fundus.

Pathological Report: 4/27/42. (Fig. 4.) The uterus measures 11.5 cm. in diameter, and when opened is seen to contain a large extensively degenerated submucous fibroid. On microscopic examination, bundles of smooth muscle cells are seen in the characteristic whorl pattern of the fibromyoma. These interlacing fibers are uniform in size and are intermingled with areas of hyaline tissue. Toward the endometrial surface, there is a moderate amount of necrotic tissue infiltrated with leuco-

cytes and red blood cells. Over the surface of the fibroid and invading it to a moderate degree, are areas of lawless glandular proliferation. The glands are increased in number, and their epithelium is definitely stratified. Numerous mitotic figures are present in markedly hyperchromatic nuclei.

Diagnosis: Degenerating submucous fibromyoma and adenocarcinoma.

Management: Following her discharge from the hospital, the patient was referred to the x-ray department for deep therapy. She received a cycle of deep therapy which was begun May 18, 1942, and completed June 11, 1942, amounting to 2,000 r. to 4 pelvic portals. Vaginal smears have been taken at each follow-up visit. They have all been negative. The patient was last seen in the Strang Clinic January 4, 1943, at which time she was in excellent condition.

The spindle cell is occasionally found in a smear indicative of carcinoma, but when present in these cases, it is not solitary but appears with other more characteristic carcinoma cell forms. When spindle cells are found in the vaginal smear exclusive of all other abnormal cells, it may be considered diagnostic of sarcoma. One such case is included in this study.

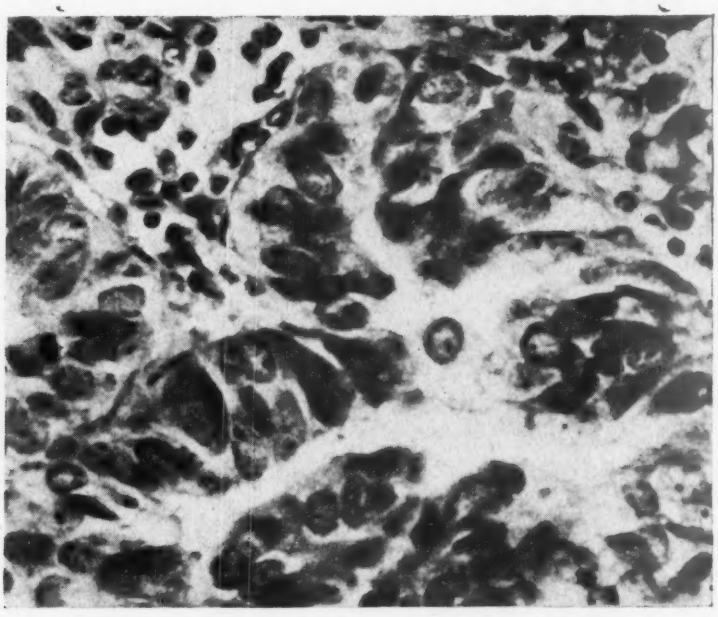

Fig. 4.—Tissue—adenocarcinoma—fundus. Magnification (×810).

CASE 3.—Mrs. H. K., aged 49 years, was first seen in the gynecological clinic of the New York Post-Graduate Hospital January 13, 1942. At this time, she complained of a bloody vaginal discharge first noticed six months previously, and hot flashes. Her menopause had occurred five years before, when a supracervical hysterectomy for uterine fibroids had been performed at another hospital. On her first clinic visit, vaginal smears and a cervical biopsy were taken.

Vaginal Smear Report: 1/13/42. (Fig. 5.) Enormous quantities of pus are seen. Many of these cells appear in thick clumps. Many deep cells indicating menopause are present. There is a moderate number of hyperchromatic cells with fragmented nuclei, and an occa-

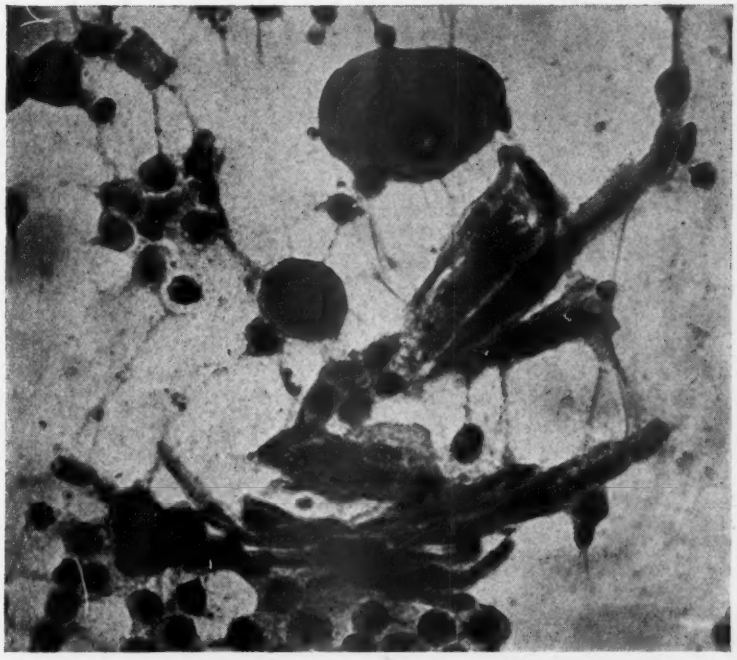

Fig. 5.—Vaginal smear—sarcoma of cervix. Magnification (×810).

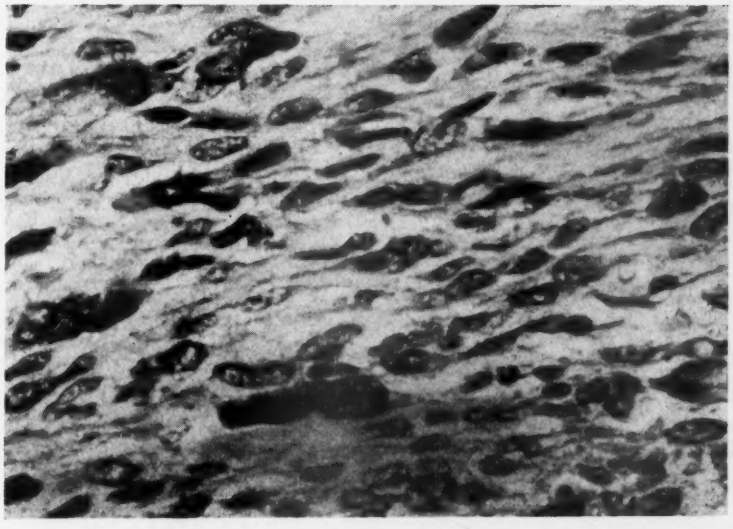

Fig. 6.—Tissue—sarcoma of cervix. Magnification (×810).

sional group of long spindle cells which do not appear malignant. The interpretation of these is obscure. Diagnosis deferred but suggestive of sarcoma.

Pathological Report: 1/13/42. (Fig. 6.) The tissue is a neoplasm consisting of interlacing bundles of smooth muscle through which courses an intricate network of a few coarse and many fine fibers of collagen and reticulum. The smooth muscle cells show many atypical features. Their nuclei vary abundantly in size, are generally large, oval or cylindrical with rounded ends. They show varying degrees of hyperchromatism. A few giant and bizarre forms are noted. An occasional mitosis is seen. A few foci of sclerosis are present with neoplastic cells isolated in thick fibers of collagen.

Diagnosis: Leiomyosarcoma of the cervix.

Management: The patient was admitted to the New York Post-Graduate Hospital and on January 14, 1942, the cervical tumor stump was excised and radium amounting to 2,080 mc. hr. was applied in six 5 mg. needles. The case has been followed since hospital discharge. Vaginal smears have been negative. She was last seen in the clinic April 13, 1943, at which time the cervix was soft, healed and free from disease.

Discussion

In this study no attempt has been made to designate through the vaginal smear undifferentiated and highly differentiated epidermoid carcinoma. All types of squamous carcinoma of the cervix produce the bizarre cell forms which are characteristic, and when these are found together with other general characteristics of malignancy, the diagnosis of squamous carcinoma is in order. Despite the fact that these aberrant forms are spectacular, it must be remembered that they constitute a relatively small proportion of the total cell elements found, and their discovery frequently requires prolonged search.

The discovery of malignant endometrial cells is attended with great difficulty. This is due to the fact that these small cells are found intermingled with dense masses of red blood cells and leucocytes. In advanced cases where the characteristic malignant fundal cell appears in large plaques, the diagnosis is somewhat simpler. The entire vaginal smear picture of endometrial neoplasm is much less impressive than that of the picture in cervical carcinoma.

Greater variations in size and shape are found in both types of cases where the lesion is advanced, but in addition to the diagnostic cell, there is ordinarily such a heavy content of blood cells and mucus that few cellular elements of any kind are distinguishable.

The apparent high incidence of malignancy in the group of patients examined is explained by the fact that of the total number of cases, approximately 57 per cent were observed at the Strang Clinics, which are exclusively confined to the study of new growths. The remaining patients were registered for endocrine disturbances at the Gynecological-Endocrine Clinic. An additional few were private patients, in whom objective symptoms suggested the possibility of malignancy. The fact that there were three instances of very early neoplasms discovered dur-

ing routine examinations of endocrine patients is of paramount importance, for it definitely illustrates the advantages of routine vaginal smears. The earlier malignant disease is brought to our attention, the sooner proper treatment can be instituted. Consequently, the ultimate number of 5- to 7-year curves should be greatly increased over the 26 per cent which prevails at present.

TABLE I. SUMMARY OF CASES

Total number cases examined			434
Total number cases followed			427
N. Y. Post-Graduate Hospital Clinic		182	
Strang Clinic		245	
Diagnosis of malignancy made from vaginal smear and Confirmed by biopsy			
Total cases			82
Strang Clinic		43	
N. Y. Post-Graduate Hospital Clinic		39	
Squamous carcinoma of cervix			48
N. Y. Post-Graduate Hospital Clinic		28	
Strang Clinic		20	
Sarcoma of cervix			1
Carcinoma of fundus			33
Strang Clinic		22	
N. Y. Post-Graduate Hospital		11	
False positive diagnoses			9
Cervix		5	
Strang Clinic	2		
N. Y. Post-Graduate	3		
Fundus		4	
Strang Clinic	3		
N. Y. Post-Graduate	1		
False negative diagnoses (all fundus)			7
Strang Clinic		5	
N. Y. Post-Graduate		2	
Cases referred without clinical diagnosis			129
N. Y. Post-Graduate Hospital Clinic		56	
Strang Clinic		93	
Cases referred with nonmalignant diganoses			251
N. Y. Post-Graduate Hospital Clinic		190	
Strang Clinic		61	
Cases referred with diagnosis of malignancy			47
N. Y. Post-Graduate Hospital Clinic		7	
Strang Clinic		40	
Total Cases			427

Summary

1. A diagnostic aid in the discovery of early pelvic malignancy has been described and the results of the method as used in 427 cases have been presented.

2. The microscopic characteristics of malignant smears have been outlined and the specific cells designating squamous carcinoma of the cervix, adenocarcinoma of the fundus and 1 case of sarcoma have been described, together with an illustrative case history for each.

3. The importance of confining the method to the realm of preliminary and corroborative procedures is stressed.

Conclusion

From the material presented, we feel justified in concluding that this procedure is worthy of continued trial. Although no claim is made for the infallibility of the test, we feel that even in its present stage of development, it represents a valuable addition to the methods now utilized for the early diagnosis of pelvic carcinoma in women. Furthermore, when suspicious cells are present, even though few in number, the patient should be further investigated. Although most are eventually proved negative, an occasional early lesion will be detected, which otherwise might have been completely overlooked.

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CERVICAL PREGNANCY

A Partial Review of the Literature and a Report of Two Probable Cases*

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CERVICAL pregnancy, admittedly of rare occurrence, has been given but scant consideration in American medical literature. Consulting three of our most widely used textbooks of obstetrics, it is found that two[1, 2] do not mention the condition, while the third,[3] denies its existence. Only one report[4] can be found since 1900 in the journals of this country.

Notwithstanding this, personal experience and a review of the literature, mainly foreign, offers convincing evidence that this type of gestation actually occurs and often presents serious complications, not infrequently terminating fatally. This unusual variety of pregnancy results from the nidation and development of the fertilized ovum in the structure of the cervix, the corpus uteri remaining uninvolved. It is to be sharply differentiated from the isthmico-cervical pregnancy described by Aufeld and Aschoff.[5] In the latter cases one finds a placenta previa with an extension into the cervix, the ovum developing in the corpus uteri. Before considering this subject any further, it might be well to outline the events which transpire in the first seven or eight days of the existence of the fertilized human ovum.

It is generally accepted, in a woman with a twenty-eight day menstrual cycle, that ovulation usually takes place between eleven and fifteen days following the onset of the preceding menstruation. It has been established by direct observation that the ovum is slowly extruded onto the surface of the ovary from the ruptured follicle, the explosive action, which one would associate with this process, being lacking.[6] The ovum is engulfed almost immediately by the fimbriated end of the tube which has been shown to assume unusual activity at this time, sweeping back and forth over both surfaces of the ovary.[7] After its entrance into the ampulla, where it is believed that fertilization most commonly takes place, the passive ovum is transported by the ciliary current and the coordinated segmental muscular movements of the tube to the uterine cavity. Its course is rapid at first, more slow as it reaches the isthmus, the total time of transportation being approximately ninety-six hours.[8] After the arrival of the ovum in the

*Presented at a meeting of the New York Obstetrical Society, Nov. 14, 1944.

uterus, it tends to lie in one of the surface crevices of the progestational endometrium in the upper part of the uterine cavity. It is a completely passive object and, while it has changed from a unicellular to a multicellular structure, its total bulk is no greater than when it first emerged from the ovary. It is still enclosed in the zone pellucida. The uterus at this stage of the progestational phase is atonic so that it is not surprising to find, in the two or three days that remain before nidation, that the ovum usually does not move far from the uterine opening of the tube. The development of the human ovum up to this point has not been observed but is believed to follow closely that noted in the rhesus monkey.[9] At the end of this time, the zone pellucida disappears and the ovum, having reached the point of development termed the blastodermic vesicle, begins to enter the progestational endometrium by a process of digestion and erosion of this structure.[10] Whether it embeds on the anterior or posterior surface of the mucous membrane probably depends upon which of these surfaces is in closest relationship to the embryonic pole of the ovum, which always presents as a spearhead of invasion.

It is impossible to believe that the intrauterine position of this minute structure, the fertilized ovum, can be influenced by gravity, sandwiched as it is between two layers of a succulent progestational endometrium which lines the extremely atonic uterus. Nevertheless, one of our most used textbooks[11] seriously discusses the effect of gravity on the position of the unembedded ovum as if it were a die in a dice box.

The fact that the ovum usually travels only a short distance after its delivery by the tube into the uterine cavity is borne out by the position of the placenta at term in the vast majority of pregnant women. It is found usually in the upper corpus attached to the anterior or posterior wall. While this is the common site of the term placenta, it may be found to be attached at lower levels in the uterine cavity. When it is attached so that it encroaches on or covers the internal os, we term the abnormal attachment placenta previa.

It is probable that many placenta previas are formed secondarily, through a persistence of a part of the chorion laeve by the process described by Hoffmeyer. In some instances, however, they result from primary nidation low in the uterine cavity close to the internal os. Occasionally such an implantation may show an extension of the placenta into the cervical canal. As an example, witness the microphotograph made from a section of curettings obtained from a patient with a two months' inevitable abortion at Bellevue Hospital a few years ago (Fig. 1). It shows chorionic villi embedded deeply into mucosa characteristic of the upper cervix. In short, the behavior of the Müllerian tract during the early days of pregnancy is such that nidation of the ovum in the most favorable upper part of the uterine cavity is almost certain. Only occasionally does this complex mechanism fail.

There remains, however, one more possibility. Suppose that the fertilized ovum, making a rapid transit of the uterine cavity under the influence of factors, unknown but probably largely accidental, enters the cervical canal before it is capable of nidation and embeds itself in the surface mucosa of this structure before reaching the external os. There is no evidence to show that the cervical mucosa possesses a special power to resist the erosive and destructive effect of the trophoblast. Neither does it possess the function of the progestational endometrium, and later the decidua, of limiting this invasive and destructive action to the superficial cellular layers of the mucous membrane. There is no reason to doubt that such an ovum can penetrate to varying depths in the cervical wall, can create a blood space by opening maternal vessels, and continue its development for a certain length of time.

Fig. 1.—Bellevue Hospital Accession No. 3595/35. Curettings from early abortion showing chorionic villus implanted in mucosa, whose stroma and glands resemble these of the isthmus or upper cervix.

Referring to the literature, a very interesting group of cases, almost entirely confined to the European journals, is found to support this theoretical possibility. These cases can be divided into two groups, in the first of which the presence of a cervical pregnancy is backed by pathologic evidence, in the second of which such a gestation is to be suspected on clinical evidence, more or less well defined.

TABLE I. CASES OF CERVICAL PREGNANCY PROVED BY PATHOLOGICAL EXAMINATION OF UTERUS (OPERATIVE SPECIMENS OR AUTOPSY)

AUTHOR, YEAR OF REPORT	AGE, PARITY	DURATION OF PREGNANCY	BLEEDING IN EARLY WEEKS	ENLARGED CERVIX	CORPUS NOTED ABOVE CERVIX	PREOPERATIVE DIAGNOSIS	TREATMENT	TRANSFUSION	RESULT	PATHOLOGY
1. Tarnier, 1887[12]	39 P.0. G.1	Term 40 wk.	?	Cervical fibroid presenting at exter. os.	0	Labor obstructed by fibroid	Cesarean section	0	Died 2 hr. P.O.	Autopsy: Small corpus above distended thin cervix containing fibroid and placental site
2. Franz, 1899[13]	41 ?	6 to 8 wk.	+	+	+	Cancer of cervix	Total hysterectomy	0	Recovery	Path.: Placenta implanted in cervix
3. Pankow, 1910[14]	46 P.9	20 wk.	+	Enlarged and expanded	+	Late abortion	1. Manual removal of placenta 2. Tamponade (twice) 3. Total hysterectomy	0	Recovery	Path.: Placenta inserted in anterior wall of expanded cervix. No decidua in corpus
4. Jaschke, 1910[15]	39 P.7	12 wk.	+	Enlarged cervix	Corpus retroverted	Abortion	1. Tamponade 2. Vaginal hysterotomy 3. Total vaginal hysterectomy	0	Recovery	Path.: Placenta inserted in anterior wall of cervix. Slight decidual reaction in corpus
5. Goodman, Rubin, 1911[4]	28 P.2 G.5	16 wk.	0	+	0	Ruptured ectopic	Supravaginal hysterectomy. Removal of placenta from cavity in cervix	0	Recovery	Path.: Placenta implanted in right side of cervix. Decidua in corpus
6. Tiegel, 1915[16]	36 P.3 G.6	12 wk.	+	+	+	Abortion	1. Packing 2. Curettage of cervix 3. Total hysterectomy	0	Died Sepsis	Path.: Placenta implanted in cervix. Decidua in corpus

7. Reinhardt, 1924[17]	24 P.0 G.1	8 wk.	0	+	+	Abortion	1. Curettage 2. Tamponade 3. Total hysterectomy	0	Recovery	Path.: Placenta implanted in right side of cervix. No decidua in corpus
8. Bacialli, 1926[18]	36 ?	12 wk.	+	+	0	Abortion	1. Curettage 2. Tamponade 3. Total hysterectomy	0	Died 4 days anemia	Path.: Placenta implanted in cervix. No decidua
9. Gans-bauer 1927[19]	32 P.1 G.2	22 wk.	0	+	Noted at operation	Placenta previa	Total hysterectomy	0	Recovery	Path.: Placenta implanted in cervix. Decidua scanty in corpus. Diverticulum of membranes in corpus
10. Meyer, 1929[20]	27 P.0 G.1	12 wk.	0	+	(Thought to be fibroid) +	Early pregnancy	1. Cervical hysterotomy 2. Total hysterectomy	0	Recovery	Path: Placenta implanted in posterior cervix. Decidua in uterus
11. Kleiner, 1929[21]	23 P.1 G.3	10 wk.	+	+ Mainly right side	+	Incomplete abortion	1. D. & C. 2. Tamponade 3. Total hysterectomy	0	Recovery	Path.: Placenta implanted in cervix on right
12. Cousse, 1934[22]	37 P.7 G.8	16 wk.	+	+	+	Late abortion	D. & C.	0	Died	Path.: Placenta implanted in cervix. (Post-mortem hysterectomy)
13. Schürger, 1937[23]	32 P.2 G.3	10 wk.	+	+	+	Hematoma of cervix	1. D. &. C. 2. Resection of cervix	0	Recovery	Path.: Placenta implanted in cervix
14. Desirotte, 1940[24]	38 P.0 G.1	12 wk.	+	+	+	Cervical fibroid	Total hysterectomy	0	Recovery	Path.: Placenta implanted in cervix

The first group of cases, numbering fourteen, has been summarized in Table I. In all of these cases, except two,[4, 23] the relationship of the placenta solely to the cervix was established beyond doubt by pathologic examination of the entire uterus, obtained by operation or on post-mortem examination.

A consideration of these proved cases of cervical gestation discloses that the patients varied in age from twenty-three to forty-six, ten of the fourteen women being over thirty, and eight out of the ten being over thirty-five. Eight of them were multiparas; four were primiparas, while in two instances the parity of the patient was not stated. In only one of the multiparas was there a history of a previous obstetrical complication; this patient[19] carried her previous pregnancy to term, the fetus being delivered by a destructive operation through an incompletely dilated cervix. There is nothing in the history of these patients, except a tendency to belong to an older age group, to suggest an etiological factor other than an accidental one.

As one would expect from the unfavorable nidation site, the ovum rarely develops to term, Tarnier's[1] case being the only exception. In ten of the fourteen cases the pregnancy was terminated at or before the sixteenth week because of the chief complication, hemorrhage. In Meyer's[20] patient the character of the pregnancy was accidently discovered during the course of a therapeutic abortion performed at the twelfth week. The longest that the two[14, 19] remaining patients carried their pregnancies was twenty-two weeks.

The commonest symptom in the early weeks was vaginal bleeding in varying amounts. The onset was sometimes so early that no history of amenorrhea was obtained, obscuring the diagnosis of pregnancy. Early bleeding was absent in four cases,[4, 17, 19, 20] being present in nine, while in one patient[12] this detail of the history was ignored. When present, the bleeding tended to become more profuse as the pregnancy grew older, eventually compelling medical intervention. The other symptoms noted were principally vague lower abdominal discomfort and backache, and occasional disturbances of urination.

Examination of these patients showed the systemic evidence of hemorrhage if bleeding had been profuse. In the patient whose pregnancy had proceeded beyond the third month, abdominal examination revealed a mass, rising from the pelvis, corresponding in size to the duration of the pregnancy. Above this mass and attached to it was sometimes noted the firmer, smaller uterine corpus, which usually was mistaken for a uterine fibroid. Except in the case reported independently by Goodman and Rubin, in whom the main signs detected were those of intraperitoneal hemorrhage, no other abdominal signs were present.

On bimanual examination obvious uterine bleeding was present. The striking finding was enlargement and expansion of the cervix which, naturally, progressively increased in size with the duration of the

pregnancy. Its consistency usually misled the examiner into believing that it was the pregnant corpus. When such pregnancies proceeded beyond the twelfth week, the external os was often found to be partly dilated, enabling the examiner to feel the sac, just above the opening, and sometimes the lower edge of the placenta.[19] In nine instances the small, firm corpus could be made out above the cervical mass. On one occasion this peculiarity could not be observed because of retroversion of the uterus.[15] Except for the absence of a history of preceding painful expulsive uterine contractions the findings were often similar to those noted in the cervical stage of the abortion of a normally implanted ovum.

The diagnosis entertained in most instances was that of early or late uterine abortion. Early placenta previa was considered in one patient, while in another, who had exhibited no bleeding, normal uterine pregnancy complicated by fibromyomata was thought to exist. In the early cases with bleeding from the onset and no amenorrhea, the presence of a cervical neoplasm was suspected on two occasions.[13, 24] In one patient, because of the signs of intraperitoneal hemorrhage, the diagnosis of ruptured tubal pregnancy was made.[4]

In eight of the patients attempts were made to evacuate the products of gestation by the vaginal route. When closed, the external os was dilated, and once vaginal hysterotomy was employed.[15] Removal of the placenta proved difficult and usually could only be accomplished in piecemeal fashion. Profuse violent hemorrhage immediately occurred which proved difficult or impossible to control with tamponade. This necessitated the performance of total abdominal or vaginal hysterectomy in six patients,[14-18, 21] while in one, the bleeding was controlled by cervical amputation.[23] The eighth patient died almost immediately of hemorrhage and shock.[22] Of the six remaining patients four were treated with total hysterectomy,[13, 19-20, 24] usually carried out under mistaken diagnosis, one was delivered by Cesarean section performed through the thin, expanded cervix,[12] while one was treated by supravaginal hysterectomy;[4] the hemorrhage from the cervical stump being controlled by mass ligation of tissue. It is striking to note that not once was transfusion utilized in this group of individuals, most of whom suffered from acute and massive blood loss.

Four[12, 16, 18, 22] of the fourteen patients failed to survive, a mortality of almost 30 per cent. The cause of death was hemorrhage and shock principally, but in one instance,[16] severe infection played an additional part in the death of the patient.

The pathologic findings are of considerable interest. Tarnier's[1] case showed at autopsy a greatly distended, thin-walled cervix containing a large cervical fibroid and the placental site. It was surmounted by a firm contracted corpus uteri, quite uninvolved in the pregnancy. The only chance of saving this patient would probably have been the per-

formance of a complete hysterectomy after the removal of the fetus by Cesarean section. Goodman and Rubin's[4] case is of interest mainly from the viewpoint that the corpus shows a well-developed decidua but no evidence of chorionic invasion. The first evidence of chorion was encountered in the upper cervix which was removed with the body of the uterus.

Schürger's[23] specimen, obtained by amputation of the cervix, shows the nidation site deep in the cervical wall and apparently about to rupture into the lateral vaginal fornix. At operation the cervix was noted to be asymmetrically enlarged and deep blue in color.

In the remaining specimens the whole uterus was available for examination. In all of them the placental implantation appeared to be confined to the cervix. However, owing to the fact that preliminary operative procedures had been utilized at varying intervals before the removal of the uterus in all but one patient,[19] in only the latter instance was the specimen intact. A decidual lining of the corpus could not always be demonstrated especially when the hysterectomy was performed some time after preliminary curettage, but was generally noted when the uterus was promptly removed.[4, 15, 16, 19, 20]

Examination of the cervix showed no evidence of cervical glands beneath the placental site, the chorionic villi penetrating and being directly attached to the cervical muscularis. The cervical muscularis was very thin, particularly in the more advanced pregnancies but was usually not deeply invaded, the ovum expanding in the direction of the cervical canal. However, in Rubin's case perforation of the supravaginal cervical wall occurred into the base of the broad ligament; while in Schürger's[23] case, such a perforation had almost taken place into the lateral vaginal fornix. Abundant large vessels, both arterial and venous, were present in the cervical wall. These findings readily explain the difficulty in removal of the placenta and the violent hemorrhage which follows such efforts.

Here can be mentioned a case, reported by Connors et al.,[25] which was not included in Table I because of its remarkable character. A forty-four-year-old woman, who had undergone a supravaginal hysterectomy three years previously and who had subsequently showed amenorrhea, was admitted to a hospital for lower abdominal pain and a yellowish discharge. On examination the cervix was found to be effaced, the external os being dilated to 4 to 5 cm. A fetal head presented. The fetus was delivered and survived for over thirty hours, weighing 896 grams. The placenta did not separate. On attempting to remove it, it was found to be densely adherent to a thin-walled cavity. It was removed piecemeal and incompletely, accompanied by profuse hemorrhage which was controlled by packing. Because of continued bleeding the abdomen was opened. A large thin-walled sac, centered in the pelvis, was found which was continuous with the cervix and to which both tubes and ovaries were attached. This was removed. Pathologic examination showed the wall to be made up of

smooth muscle. No glands were identified. Connors interpreted this case as a left tubal pregnancy which developed to the sixth month. He thought that tubal contractions had brought about the dilatation of the cervix. In the light of the cases just reviewed it would seem more likely that this represents an instance of cervical gestation, following supravaginal hysterectomy, and the development of continuity between the lumen of a tube and the cervical canal.

The second group, also fourteen in number, has been summarized in Table II. These patients all escaped radical operation, the pregnancy having been evacuated by the vaginal route, with successful results except in two instances, in spite of the fact that transfusion was only used in one patient.[34] The details of these cases conform in the main with the features which already have been emphasized in the discussion of the data in Table I. Of course, one must depend on the clinical observations of those who reported the cases and certainly, in some instances, the evidence is not too strong. Wolters'[26] second case, a fatality, is so scanty in detail that one must discard it from consideration. Case 1 of Tropea,[28] Case 2 of Bolaffi,[29] and the case reported by Hyslop[30] suggest strongly that the condition encountered was the cervical stage of an ordinary uterine abortion, because of the absence of evidence of any strong attachment of the placenta to the cervical wall and because the removal of the ovum was not followed by violent hemorrhage. In two of the above cases the description of the ova suggests advanced degeneration. The remainder strongly suggest that the pregnancy was fully implanted in the cervical canal.

Excluding the four cases mentioned above, the maternal mortality amounts to about 10 per cent. Combining both groups of cases the mortality is found to be a little more than 20 per cent.

The cases summarized in these tables do not pretend to represent a full review of the literature and, undoubtedly, other reports on this condition have escaped notice. It is believed that many such cases escape diagnosis, or if recognized, are not reported in the literature.

Interest in this rare type of pregnancy was stimulated by the observation of two patients in whom all the clinical evidence points to the primary nidation site as being in the cervix. Unfortunately, no pathologic evidence accompanies these records so that they only can be considered presumptive instances of cervical gestation.

Case Reports

Case 1.—Mrs. F. R., aged 40, para i, gravida ii, was first seen on January 23, 1939, complaining of irregular bleeding. Her first pregnancy occurred in 1927 and was normal. She was delivered at term by breech extraction. This child had died at the age of seven from mastoiditis.

Her menses had always been regular, appearing at twenty-eight-day intervals, lasting four days with no pain. The last normal period had occurred December 1, 1938. About December 8, she began to have slight vaginal staining which had recurred at intervals. Her breasts had been swollen and tender and she had suffered from slight nausea.

TABLE II. CASES OF CERVICAL PREGNANCY BASED ON CLINICAL EVIDENCE

AUTHOR, YEAR OF REPORT	AGE, PARITY	DURATION OF PREGNANCY	BLEEDING IN EARLY WEEKS	ENLARGED CERVIX	CORPUS NOTED ABOVE CERVIX	PREOPERATIVE DIAGNOSIS	TREATMENT	TRANSFUSION	RESULT	REMARKS
1. Devreigne, 1911[12]	39 P.2 G.6	26 wk. Fetal death at 16 wk.	0	+	+ (Thought to be fibroid or accessory horn)	Late missed abortion	1. Manual and instrumental removal (incomplete) 2. Tamponade	0	Recovery	Placenta implanted in expanded cervix. Corpus above, empty
2. Wolters, 1924[26]	26 P.3 G.6	20 wk.	+	+	Noted at operation	Late abortion	1. Manual removal 2. Tamponade	0	Death	Fetus removed through partly dilated exter. os. Placenta removed piecemeal from cervical wall. Corpus above, empty
3. Wolters, 1924[26]	? ?	12 to 14 wk. Fetus expelled	?	?	?	Late abortion	Placenta removed piecemeal with instruments	0	Death	Placenta removed piecemeal from distended cervix. Character of corpus not noted
4. Baccialli, 1927[18]	25 P.1 G.2	6 wk.	+	+	+	Early abortion	1. Tamponade 2. Curettage and tamponade	0	Recovery	Aborted part of early ovum. Profuse hemorrhage not controlled by packing. Inspection and curettage of cervix; packing. Curettings showed no chorion
5. Baccialli, 1927[27]	32 P.0 G.1	8 wk.	0	+	+	Cervical pregnancy	Cervical hysterotomy	0	Recovery	Cervix incised and ovum removed. Implantation site seen in cervical canal
6. Tropea, 1929[28]	29 P.2 G.4	12 wk.	?	+	Retroverted	Early abortion	Dilatation and curettage	0	Recovery	Size and character of ovum suggests degeneration. Attachment to cervix not convincing

7. Tropea, 1929[28]	38 P.6 G.15	16 wk.	0	+	+	Late abortion with ruptured membranes	1. Tamponade 2. Manual removal	0	Recovery	Placenta adherent to left side of cervical canal. Fundus above, empty
8. Bolaffi, 1932[29]	37 P.1 G.2	6 to 8 wk.	+	+	+	Abortion	Dilatation and curettage	0	Recovery	Cavity identified in cervical wall. Corpus above and empty
9. Bolaffi, 1933[29]	39 P.1 G.2	8 wk.	0	+	+	Early abortion	Dilatation and curettage	0	Recovery	Ovum protruding from external os. Implantation site identified in cervical canal
10. Hyslop, 1935[30]	35 P.0 G.1	8 to 10 wk.	0	+	+	Early abortion	Dilatation and curettage	0	Recovery	Ovum apparently implanted in cervix. Description suggests degenerating early pregnancy
11. Iolkin, 1936[31]	35 P.0 G.3	18 to 20 wk.	0	+	+	Late abortion	1. Dilatation of cervix 2. Manual and instrumental removal of placenta 3. Tamponade	0	Recovery	Placenta implanted in distended cervix. Piecemeal removal. Cavity of corpus identified above
12. D'Aprile, 1937[32]	32 P.1 G.2	8 wk.	+	+	+	Early abortion	1. Dilatation and curettage 2. Tamponade 3. Tamponade 4. Curettage	0	Recovery	Ovum implanted in canal. Removed with difficulty from posterior wall. Path.: Villi invading cervical tissue
13. Wittrin, 1938[33]	29 P.2 G.4	8 wk.	+	+	+	Early abortion	1. Dilatation and curettage 2. Tamponade	0	Recovery	Ovum firmly attached to wall of distended cervix. Corpus identified above, empty
14. Reist, 1941[34]	34 P.3 G.6	23 wk.	0	+	+	Late abortion	1. Manual removal (incomplete) 2. Repeated tamponade 3. Manual removal (14th day) complete	+	Recovery	Rupture of amniotic sac with passage of fetus. Placenta implanted on posterior left side of distended cervical canal. Corpus above, empty

Examination showed a healthy, well-developed, middle aged female. General examination proved quite normal. Pelvic examination showed a parous introitus and excellent pelvic support. The cervix was posterior, slightly enlarged, soft and normal in appearance. On speculum examination no evidence of bleeding was present. On bimanual examination the corpus was in anterior position, slightly enlarged and soft. The adnexa were negative. No tenderness was present. The findings were suggestive of an early uterine pregnancy. An Aschheim-Zondek test was performed which was reported as positive. She was advised to limit her activity, spending as much time resting as possible.

She was next seen on February 24, and in the meantime noted slight bleeding on several occasions, not accompanied by cramps or pain. Since the corpus uteri could be palpated abdominally just above the symphysis, a vaginal examination was not performed.

On March 11, and again on March 13, she observed slight spotting and shortly after the last occasion passed a quantity of clear fluid per vaginam, without experiencing any other discomfort. Reporting this incident, she was advised to enter the Sloane Hospital immediately (Case No. 574807). On examination after admission, the fundus uteri could barely be felt abdominally. On bimanual examination, the cervix was posterior and gave the impression of being flush with the vaginal vault and fully retracted. The supravaginal cervix was greatly expanded, the uterine mass approximating in size a three and one-half months' pregnancy. The external os was a finger tip dilated with a very thin margin and just above it the fetus could be palpated. No bleeding was taking place, but amniotic fluid was escaping. In spite of the absence of show or painful contractions, these findings suggested a late inevitable abortion, in which the ovum had been forced into the expanded upper cervix. It was expected that the process would be easily completed with the stimulation of contractions by means of pituitrin. However, this anticipated result failed to occur in spite of repeated injections of this agent over the next six days. Slight cramps followed each injection and slight intermittent vaginal bleeding occurred. Examination showed no change in the condition of the cervix. On March 19, she suddenly developed a fever of 103.8° F. accompanied by a shaking chill. Because of this evidence of amniotic sac infection, it was decided to empty the uterus surgically.

Examination under gas oxygen anesthesia revealed the same findings as have previously been described. No bleeding was evident. The thin rim of cervix about the external os was dilated easily, permitting the delivery of a three and one-half months' fetus. The placenta which appeared firmly attached was then grasped with a sponge stick and removed. A sudden, violent and profuse hemorrhage, estimated at well above 1,000 c.c. followed this procedure, and was controlled with difficulty by packing. This incident prevented a more careful investigation of the exact location of the placenta. The patient recovered consciousness rapidly following the termination of anesthesia, but showed a mild degree of shock, her pulse being rapid and soft and the blood pressure was 90/60. She was given a 500 c.c. transfusion and was returned to her room in fair condition. The following day a blood count showed 2,740,000 red cells and a hemoglobin of 56 per cent. The packing was partly removed on March 20, and completely on March 21. She had one more chill accompanied by a rise in temperature to 102° F. A culture from the amniotic sac taken at the time of operation showed streptococcus viridans. She was given sulfapyridine, but this was discontinued in a few days

when her temperature fell to normal. A second transfusion of 500 c.c. was given on March 21, following which her blood count rose to 3,140,000 with 66 per cent hemoglobin. Although slight bleeding continued she was allowed out of bed on March 28, nine days after the evacuation of the uterus. Shortly after this the vaginal bleeding increased, and she began to pass large clots. A rise in pulse and pallor soon appeared. She was returned to the operating room, given a transfusion of 500 c.c. and examined under anesthesia. The cervix was found to be widely dilated, the entire cervical canal being greatly expanded. On the left lateral wall was a mass of adherent placental tissue about four cm. in diameter. At the summit of this space was a constriction through which the examining finger could be passed into the cavity of the corpus uteri, which felt perfectly smooth. The removal of the adherent placental fragments by sponge stick was attended again by sudden, violent and profuse hemorrhage which was controlled by packing. The patient, however, went into deep shock with an almost imperceptible pulse and a blood pressure of 70/16. A second 500 c.c. transfusion was given following which her condition gradually improved so that at the end of eight hours, it was possible to return her to her room.

The packing was partly removed on March 30, and wholly on March 31. Barring moderate fever for a few days and a marked secondary anemia, for which she was given a 750 c.c. transfusion on April 2, her recovery was uneventful. She was discharged twenty-eight days after admission on April 10, 1939, with a red count of 3,400,000 and a hemoglobin of 73 per cent. Normal findings were present on pelvic examination. She has been seen on several occasions since this date and presents nothing noteworthy as regards to either symptoms or physical findings.

In this patient the possibility of cervical pregnancy was not considered until the uterus had been explored the second time. However, there were a number of striking features which were noted before this procedure was carried out and which made no impression on this observer because he had never seen or heard of cervical gestation. Following rupture of the membranes, examination showed the greatly expanded and enlarged cervix of an incomplete abortion. However, there was a complete absence of any of the painful uterine contractions, which must precede such a stage. Moreover, there had been no bleeding other than the slight occasional staining which had been noted ever since the pregnancy had first been suspected. The use of pituitrin on several successive days failed to produce the result which one might confidently expect if the patient had a corporeal abortion. Repeated examinations failed to show any evidence that the presumed uterine abortion was pursuing its expected course.

The fact that the corpus surmounted the cervical mass escaped notice until the final examination under anesthesia but must have been detectable at a much earlier time. Such observations are not in the least characteristic of corporeal abortion and if encountered again by this observer will lead him to suspect a cervical gestation with rupture of the sac into the cervical canal. This case resembles the majority of the instances summarized in Tables I and II.

Case 2.—Mrs. A. G. (Chart No. 206774), was admitted to Bellevue Hospital on January 10, 1942, complaining of profuse vaginal bleeding. Her last menstrual period had occurred in October, 1941. The course of her pregnancy was uneventful until a few hours before her admission, when she developed severe backache and began to bleed profusely from

the vagina. She repeatedly denied any attempt at induction. Her temperature was normal and her pulse 100. Her red blood count was 3,000,000; hemoglobin 64 per cent; sedimentation rate normal; and urinary findings negative.

General physical examination revealed no noteworthy findings. Abdominal examination was negative. Pelvic examination showed a nulliparous introitus and excellent support. The cervix was posterior and one finger dilated. In the right posterolateral aspect of the vaginal cervix was an irregular lacerated area from which protruded a large mass of placental tissue; this was removed. Exploration of this laceration with a finger revealed a cavity in the wall of the cervix which did not pass upward and which was separated from the cervical canal by a thin septum. The uterine corpus was anterior and was moderately enlarged. The adnexa and parametrial areas were normal. At the end of this examination bleeding was only moderate. There is no way of determining the appearance of this cervix before the rupture occurred, but undoubtedly it must have been asymmetrically expanded and enlarged. The patient appeared in mild shock and received a transfusion. Complete hysterectomy was recommended unless bleeding ceased. Unfortunately, for the complete elucidation of this case, bleeding soon stopped and the patient pursued an uneventful afebrile course in the hospital.

Before discharge examination showed the cervix to be firm and closed. The corpus was in anterior position and well involuted. The adnexa and parametrial tissues appeared normal. On the right lateral aspect of the cervix was a healing laceration which bled slightly on manipulation.

Histological examination of the placenta showed it to be made up of fresh, well-preserved villi.

This patient returned to the Hospital on July 12, 1943, when she was delivered of a normal term infant by low forceps. Bilateral lacerations of the cervix of moderate extent were noted and repaired. Otherwise the cervix appeared normal.

As an alternative to classifying this patient as a cervical pregnancy, one might consider her to be an example of a crudely performed induced abortion. The location of the cavity in the cervical wall without communication with either corpus or cervical canal is against this; as well as the normal course pursued by the patient once the abortion was complete. This case is a probable example of the termination of a cervical pregnancy by rupture into the vaginal fornix. This case is very similar to the one reported by Schürger.[23]

Comment

It seems probable from the evidence which has been presented that, on rare occasions, the fertilized ovum transverses the uterine cavity before the seventh day of development and, having reached the cervical canal, embeds itself in its mucosa. The depth to which it penetrates is variable as is the level at which it undergoes nidation. Probably complete penetration of the mucosa takes place, since the chorion frondosum develops in relation to the muscularis. It seems likely that many of these pregnancies may terminate in abortion at a very early stage because of the unfavorable site of nidation and so escape recognition. In most instances, when the development continues, the ovum

expands towards the cervical canal carrying before it the mucosa which functions as a decidua capsularis. Very probably early degenerative and necrotic changes occur in the overlying mucosa, which is not functionally adapted to such a process. This may account for much of the early bleeding. With the gradual expansion of the ovum the cervix becomes a thin-walled globular structure, on the summit of which can be felt the corpus, slightly enlarged and firm, and uninvolved in the gestation. In response to the pregnancy the cervix becomes highly

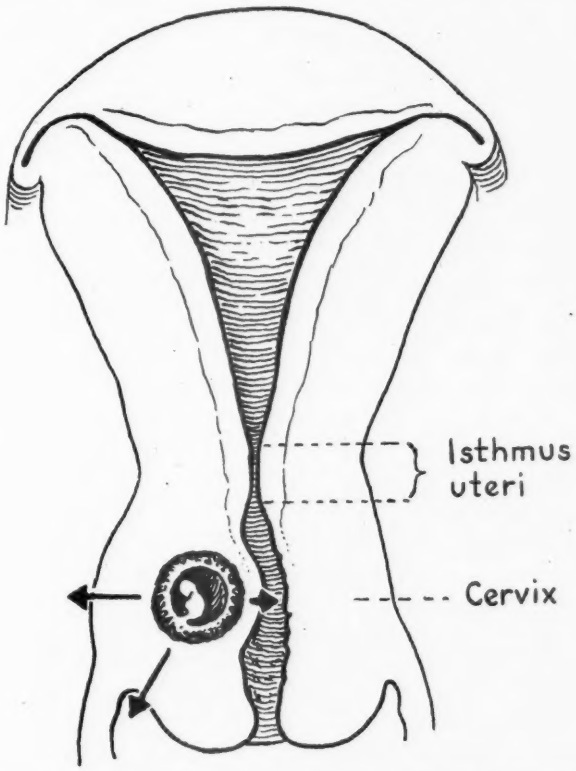

Fig. 2.—Diagram showing four weeks' old ovum implanted in cervix. Further development leads to (1) expansion of cervical mucosa overlying nidation site in character of cervical canal; or (2) rupture of infra- or supravaginal cervix if the cervical muscularis is deeply invaded by chorion.

vascularized; the external os may become dilated. Less commonly, the chorionic invasion may so damage the cervical muscularis by penetration that rupture is imminent or may actually take place. When the lower cervical wall is weakened, rupture can take place into the vault of the vagina. When the upper cervical wall is attenuated, rupture can take place either into the base of the broad ligament, or beneath the bladder, or into the cul-de-sac with the formation of hematomas or intraperitoneal hemorrhage. (Fig. 2.)

Commonly, this type of pregnancy invites surgical intervention before the fourth or fifth month by the occurrence of profuse hemorrhage, by

rupture of the amniotic sac, or by actual perforation of the cervical wall. Unless careful observation reveals the unusual characteristics of a cervical gestation, the diagnosis will usually be missed. On attempting to remove the placenta, it is found to be firmly attached and comes away in fragments and incompletely. Violent hemorrhage, difficult to control with tamponade, accompanies these measures. In the proper management of such cases repeated transfusions, in large quantities, are necessary. With them, the usual case of cervical pregnancy may be evacuated by the vaginal route with a fair degree of safety. When, however, such a pregnancy has proceeded past the fourth month complete hysterectomy may be the safer approach to this problem.

In closing, it is to be emphasized that cervical pregnancies may be regarded as rare and unusual types of ectopic pregnancy. The placental attachment has certain of the features of placenta accreta. The cervix seems only slightly more adaptable than the Fallopian tube to the nidation of the ovum and the continuation of the pregnancy to term. Fortunately, cervical pregnancy is far rarer than tubal gestation, since it is much more difficult to treat from a surgical point of view.

Conclusions

1. Cervical pregnancy is a definite, though rare, entity. Many cases may be unrecognized.

2. Such pregnancies are rarely carried beyond the twentieth week of gestation. Usually it is necessary to intervene surgically before the fifth month because of hemorrhage, rupture of the amniotic sac, or perforation of the cervical wall.

3. Profuse and violent hemorrhage accompanies the attempt to remove the placenta.

4. Enlargement and expansion of the cervix accompanied by bleeding in the early months of pregnancy, the detection of the corpus uteri surmounting the cervical mass should be regarded as suggestive of this condition.

5. Supravaginal rupture of the cervix should be treated by prompt and radical surgery.

6. Intravaginal rupture of the cervix can sometimes be treated more conservatively; however, this complication may require cervical amputation or complete hysterectomy to control hemorrhage.

7. When perforation is not present, in most instances the placenta can be evacuated; partially or completely, either manually or instrumentally; the hemorrhage can be controlled by packing.

8. Blood for transfusion should be available in quantity to combat the large blood loss which may be expected in cases treated by placental removal.

9. With the use of large and repeated transfusion, it is believed that the need for radical operation in the treatment of this condition can be sharply reduced.

10. However, on the rare occasion when such a pregnancy progresses beyond the fourth month, complete hysterectomy may well be the safer approach.

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THE ROLE OF THE INTERMITTENT CONTRACTIONS OF THE UTERUS IN THE PROCESS OF LABOR

Observations Made With the Lóránd Tocograph

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IT IS taken for granted universally that the intermittent contractions of the uterus are essential to the process of labor. And included in this assumption is the belief that they probably play a role in the advancement of the first, as well as in that of the second stage of labor. No doubt the first of these opinions is based largely upon the further supposition that intermittent contractions invariably accompany labor, and to a less extent on the observation that prolonged labors, not due to disproportion, are accompanied by contractions of poor quality.

Certain observations upon the motility of the uterus during labor, made with the tocograph, are of interest in connection with the above considerations.

Observations

Among the tracings of the uterine activity secured from some 1,800 patients when in labor, we possess the records of two individuals who experienced no intermittent contractions. These two observations are as follows:

Absence of Intermittent Contractions During Labor in Association With Abruption of the Placenta

CASE 1.—Fig. 1 reproduces the tocographic records of a patient who was experiencing an abruption of the placenta during labor; the details of this experience have been described previously.[1] Although this patient exhibited no detectable intermittent contractions after the abruption of her placenta had taken place, she delivered her infant spontaneously per vaginam. Her uterine tone, however, was unusually high throughout labor, and no doubt it was the existence of this high tone that made it possible for the labor to proceed.

Absence of Intermittent Contractions During a Normal Labor

CASE 2.—Mrs. R. J., a colored primipara, aged 28, had an uneventful pregnancy except for a slightly excessive gain in weight. Her pelvis was of normal size, and her expected confinement date was November 2, 1943.

Her membranes ruptured spontaneously without pain at 4 P.M. on November 14, and she was admitted at once to the hospital. Her uterus was unusually tense, but was exhibiting no intermittent contractions.

The fetus presented in the R.O.T. position; the head was engaged and the cervix was dilated 8 to 9 centimeters.

Pain began at 7 P.M. November 17. This was described as a belt of pain below the umbilicus, beginning in the back and radiating forward. It was described further as being intense and deep. It would ease slightly at times sufficiently for her to get her breath, and increase again immediately, but was never absent. This was the only painful sensation which she experienced. After her labor, the patient volunteered the statement that she believed that she had never experienced true labor pains as they had been described by friends.

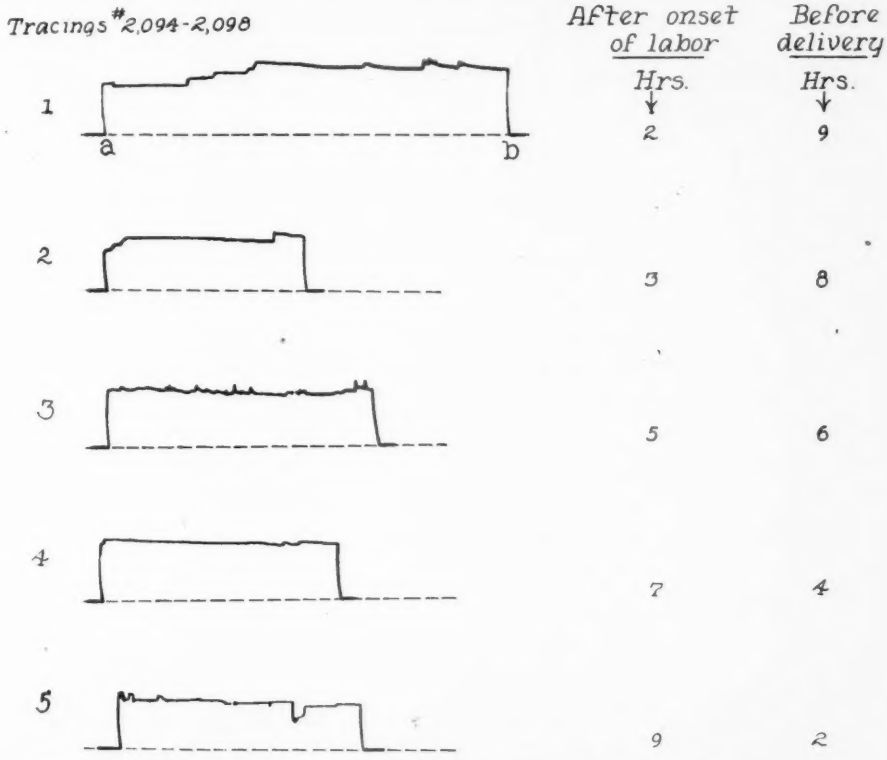

Fig. 1.—Showing the uterine motility throughout labor of a patient experiencing abruption of the placenta. Observations recorded through the medium of the abdominal wall by means of a Lóránd tocograph. Machine placed on abdomen at *A* end of each tracing and removed at *B* end. Note absence of intermittent contractions, but unusually high tone which is indicated by height of graphs above their base lines.

The uterus remained uniformly and unusually tense for 40 hours, and exhibited no palpable intermittent contractions during long periods of continuous observation. A series of tocographic records, reproduced in Fig. 2, was secured at irregular intervals during this period. None of these tracings reveals the presence of any intermittent contractions.

The amniotic fluid became discolored. Vomiting occurred repeatedly, and the patient's temperature rose. In view of her general condition, and because the fetus failed to progress, delivery was decided upon.

The patient took her anesthetic poorly, becoming cyanotic. At this time the fetal heart sounds disappeared. The cervix hung loosely around the infant's head, which was in midpelvis in the transverse

diameter, and presented considerable molding and caput formation. Forceps were applied within the cervix and the infant was delivered without incident. It was stillborn and weighed 3,785 grams.

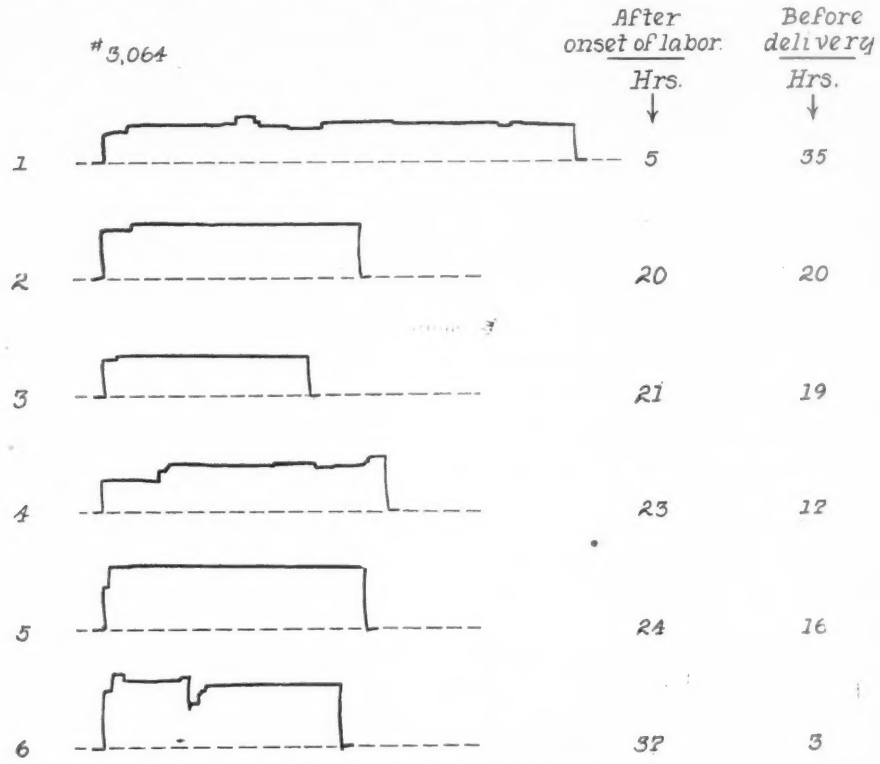

Fig. 2.—Showing the uterine motility throughout labor of a patient who experienced neither subjective nor objective evidence of the presence of intermittent uterine contractions. Note unusually high uterine tone.

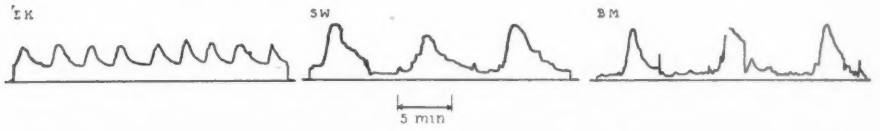

Fig. 3.—Examples of the intermittent contractions of three individuals made during the first stage of their labors. Tracing E. K. illustrates normal uterine tone and intermittent contractions which are normal with respect to: (a) frequency, (b) strength, and (c) duration. The tracings of patients S. W., and B. M. reveal a lower tone than normal. Their contractions are very much stronger than normal, and also less frequent and longer in duration than normal.

The Influence of the Contractions Upon the Duration of the First Stage of Labor

The magnitude of the uterine contractions which takes place during labor, as a rule, does not differ greatly from patient to patient. The occasional individual, however, may experience contractions of unusual strength.

Fig. 3 reproduces the tocographic tracings of three individuals taken during the first stages of their labors.

Patient E. K. (Fig. 3), was a primipara who had a labor of 27 hours' duration. Her second stage consumed 1 hour and 10 minutes. Her

tracings were made 7 hours before delivery, when the cervix was dilated only 5 centimeters. This tracing registers a normal tone and contractions which were normal in all respects. Her delivery, likewise, was normal.

Patient S. W. (Fig. 3), was a para x. Her labor lasted 12½ hours. This tracing reveals a low uterine tone, but extremely strong contractions of unusually long duration, occurring relatively infrequently. Her tracing was made 11 hours before delivery, when her cervix was dilated only 2 centimeters. The second stage of labor was short requiring less than 20 minutes.

Patient B. M. (Fig. 3), was a para v, who experienced a labor of 38 hours' duration. Her tracing was made 11 hours before delivery, when her cervix was only dilated 3 centimeters. She, likewise, had unusually powerful contractions throughout labor. The second stage of labor was short lasting less than 40 minutes.

Comments

It is quite true that labor almost universally is accompanied by intermittent contractions. The present observations, however, indicate that it may proceed to completion in the absence of such contractions. For this to take place, however, the uterine tone must be persistently high. We have never observed labor to occur in the absence of both intermittent contractions and a persistently high uterine tone.

The first stages of the two labors associated with unusually strong contractions were of average length.

The present observations thus suggest that the intermittent contractions are not indispensable to the process of labor, and that they do not play a significant role in determining the length of the first stage of labor.

In view of these findings, it would seem that any efforts to be expended in initiating labor, or in improving labors of poor quality, should be directed primarily at some more fundamental purpose than in merely trying to influence the power of the uterus to contract intermittently. Toward just what goal future researches should be directed in order to acquire a better understanding of the mechanism of labor, remains to be determined.

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THE PREVENTION OF CANCER OF THE CERVIX

Report of Second Survey

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In 1941, a report[1] was published on a survey of 10,000 cases of deep cauterization of the cervix in the Elizabeth Steel Magee and St. Francis Hospitals, Pittsburgh, Pa. This survey covered a period of twenty-five years and was finished in 1939. Before the survey, it was our clinical impression that this procedure has been effective in preventing cancer of the cervix. In the follow-up study, 3,143 replies to a questionnaire were received. Pelvic examinations were done in 1,341 of the patients. An effort was made to find out the cause of all deaths that occurred in the series, and the nature of all secondary operations. There were two known cases of cancer of the cervix following cauterization before the survey was started, and one of them is still alive. The extent of the cauterization was questionable in both of these cases.

In this first survey no other cases of cancer of the cervix were found. In an effort to determine the number of cases of cancer that should have occurred in this group, we were unable to get definite information from published statistics, or from the various cancer societies and other sources of information. We were referred to Dr. Levin,[2] whose work in this field has been outstanding and our follow-up material was turned over to him for evaluation. He estimated the expected number of deaths from uterine cancer by applying to each age group, for the period of observation, the mortality rates among women in Pittsburgh for the census year 1930. He found in the survey that the average age of the patients contacted, or who had died, was 40.1 years, and that the average period of observation was only 5.6 years. It was evident then that the largest number of the patients contacted has been operated on in more recent years. He stated that if the 3,143 patients were observed until all had died, 79 deaths from uterine cancer would be expected. Whereas, in our limited survey only 6 deaths could be expected. He stated that our follow-up carried us to the age level where cancer of the cervix should rise in incidence rapidly, and he recommended further follow-up study. In the first questionnaire, information was requested as to patient's general health and the presence of vaginal discharge or bleeding, without stating the purpose of the study.

Second Survey

In the second survey, we were more specific and explained that an attempt was being made to find out if the operation had succeeded in

preventing cancer of the cervix. This brought many more replies. Many other patients, whose letters had been returned in the first survey because of inaccurate address, were located by means of the city directory. So we now have a follow-up of 4,487 patients. No other cases of cancer of the cervix were found. The material from this survey was submitted to Dr. Levin[2] again, and we quote from his first report:

"Analysis of the tabulated results of your follow-up series shows some interesting facts. The mean age at time of first operation was 34.4 years; at time of last observation it was 42.8 years (Table I). The average period of observation was 8.7 years. Although this is still a comparatively youthful group of patients, the findings with respect to cancer are fairly striking.

TABLE I. AGE-DISTRIBUTION AT TIME OF CAUTERIZATION AND AT TIME OF FOLLOW-UP SURVEY: PATIENTS TREATED BY DEEP CAUTERIZATION OF CERVIX UTERI 1914 TO 1939

AGE GROUP (YEARS)	NUMBER IN EACH AGE-GROUP AT OPERATION	AT LAST OBSERVATION	PERSON-YEARS OBSERVATION*
14	8	0	4.00
15 to 19	170	12	447.50
20 to 24	580	116	2,068.75
25 to 29	864	345	4,609.75
30 to 34	899	633	6,556.25
35 to 39	769	762	7,208.75
40 to 44	583	802	6,656.75
45 to 49	351	696	5,219.75
50 to 54	178	570	3,348.75
55 to 59	47	297	1,713.75
60 to 64	27	149	781.25
65 to 69	8	73	308.75
70 to 74	2	20	100.00
75 to 79	1	8	37.50
80 to 84	0	3	12.50
85 to 89	0	1	2.50
	4,487	4,487	39,076.00
Mean age	34.31 ± .14	42.82 ± .15	
Mean years observation per person—8.71			

*Calculated separately from the following information: For each age-group, the numbers (a) cauterized, (b) died, (c) carried over from earlier ages, (d) carried into the next age-group, (e) observation ended by follow-up.

On the basis of cancer mortality among the female population of Pennsylvania in 1930, we calculated the number of cases of cancer of the breast, fundus uteri and cervix uteri which would be expected among the total series of 4,487 women during the period of observation. For each type of cancer the expected number of cases was estimated according to whether deaths per year are considered to represent 80 per cent of new cases or 50 per cent, giving both a low and a high value for expected cases. The figures are:

	Expected Cases	*Observed Cases*
Breast cancer	10.7 to 17.2	18
Uterine fundus cancer	3.3 to 5.4	4
(excluding hysterectomies)	2.5 to 4.2	
Uterine cervix cancer	14.5 to 23.2	2

The number of cases of breast cancer and uterine fundus cancer which was found agrees quite well with what would be expected. The number

of cervix uteri cases is about one seventh that expected, representing a reduction of approximately 85 per cent.

In considering the significance of these findings, a number of complicating factors must be considered. The expected number of cancer cases refers to what would be expected if these women were comparable in all respects to the average female population of Pennsylvania. Actually, the series differs in several respects from the general female population, and one must ask whether these differences could be responsible for the results obtained. With respect to color and marital status, the 'cauterized series' probably had a higher proportion of colored women and certainly a higher proportion of married women than would a random sample of women of the same age distribution in Pennsylvania. However, the effect of both these factors would be to *increase* the expected number of cervix cancer cases. They may, therefore, be disregarded, although it would be interesting to have exact data on color and marital status, by age, at time of first and last observation.

The chief difficulty in a follow-up study where the follow-up is incomplete is to be certain that the followed cases have not been favorably selected. For example, the follow-up series *was* favorably selected with respect to death, probably because there was less chance of hearing from or about a dead patient. The question is whether, for some unknown reason, we were *less* likely to hear from a patient with cervix cancer and *more* likely to hear from a patient with breast cancer. I can see no reason to believe this. In fact, it seems to me that the form of cancer which a gynecological service would be *most* likely to hear about, would be uterine cancer.

There are a few more calculations and tabulations which we hope to make on your material. In any event, I believe that this material as it stands should be reported. Perhaps some detail regarding the method of calculation might be of interest to others engaged in similar follow-up studies."

It will be noted that Dr. Levin has been very conservative in his estimates, for in the series he found our incidence of cancer of the breast equal to the upper estimate of expected cancer and the observed cancer of the fundus equal to the mean estimate. But in cancer of the cervix, he compares the known incidence with the lowest figures of expected incidence or 14.5 cases. Dr. Levin later wrote as follows:

"After writing you last, it occurred to me that there was a valid objection to using the *living* cases of cancer observed in your follow-up, in comparison with the expected number of cases or deaths. The reason is that the method of follow-up by questionnaire tends to *select* living patients, because obviously a living patient is more apt to "answer" a questionnaire than a dead one. This is borne out by the fact that the number of deaths from all causes which the follow-up uncovered was only about half the expected number. For that reason, I believe we are on safer ground in confining attention to deaths, in making our comparisons.

The expected deaths from various causes were calculated by applying the age-specific mortality rates for Pennsylvania (females) in 1930. This year was selected both because of the accuracy of the rates in a census year and because 1930 was close to the middle year of the observation period (1914 to 1939).

TABLE II. EXPECTED AND OBSERVED DEATHS FROM VARIOUS CAUSES, AMONG 4,487 PATIENTS FOLLOWED FOR VARYING PERIODS AFTER DEEP CAUTERIZATION OF THE CERVIX

CAUSE OF DEATH	NUMBER OF DEATHS		RATIO: OBSERVED / EXPECTED
	OBSERVED	EXPECTED*	
All causes	156	297.3	0.52
All cancer	26	44.9	0.58
Cancer of the fundus uteri†	1	2.0	0.50
Cancer of the cervix uteri‡	1	11.6	0.09
Cancer of the breast	11	8.3	1.32

*Deaths expected on basis of age-specific mortality rates among all females, Pennsylvania, 1930, applied to the person-years observed in each age group.

†Patients who had hysterectomy were not counted as exposed to risk of developing carcinoma of the fundus.

‡Patients who had total hysterectomy were not counted as exposed to risk of developing carcinoma of the cervix.

You will note, from Table II, that the number of deaths from 'all causes' observed was almost half the expected. The number of deaths from 'all cancer' observed was in approximately the same ratio. The inference is that the method of follow-up was as successful in tracing deaths from cancer as deaths from any other cause.

Considering now the deaths observed from cancer of various sites, we may compare these with the calculated expected deaths in two ways: First, on the assumption that the deaths which were traced were actually all the deaths which occurred; second on the assumption that the follow-up missed the same proportion of deaths from cancer as it did deaths from all causes. In Table III, both of these comparisons are made.

TABLE III. EXPECTED AND OBSERVED DEATHS FROM CANCER OF VARIOUS SITES AMONG 4,487 WOMEN FOLLOWED AFTER CAUTERIZATION OF THE CERVIX

SITE OF CANCER	EXPECTED* (T)	OBSERVED (O)	OBSERVED† "CORRECTED" (O)*	VALUE OF P‡ FOR T-O	VALUE OF P‡ FOR T-O*
Cervix	11.6	1	2	0.002	0.005
Breast	9.2	11	21	0.59	0.0004
Stomach	5.8	1	2	0.05	0.11
Intestines, rectum and anus	4.9	3	6	0.39	0.62
Other sites	15.0	10	19	0.20	0.30

*Calculated from age-specific mortality rates among all females, Pennsylvania, 1930, applied to person-years observation in each age-group of the 4,487 women.

†Corrected by assuming that the actual number of deaths was in the same ratio as $\frac{\text{Expected Deaths from all causes}}{\text{Observed Deaths from all causes}} = \frac{297.3}{156} = 1.906 \times$ observed deaths.

‡P = states the probability that the difference between expected and observed values would occur as a result of sampling error. Conventionally, values of P of 0.05 or greater are interpreted as indicating that random error could account for the difference found.

In the first comparison, only deaths from cervix cancer appear to be strikingly different (less) than expected. In the second comparison, deaths from cervix cancer are still significantly low, but, in addition, it appears that deaths from breast cancer were significantly higher than expected. As far as cervix cancer is concerned, even if we count the additional living case which was observed as dead and thereby raise the 'corrected observed' number of deaths to 4, the decrease is still greater than can be accounted for by sampling variation ($P = 0.0264$).

The decrease in deaths (and cases) of cervix cancer in this series becomes all the more striking when one considers that these are the cases which a gynecological clinic would be least apt to miss, in comparison to other forms of cancer, or other types of fatal illness.

This group of women differed from the general female population of Pennsylvania in the following particulars:

(1) More married women—93.0 per cent as compared to 65.7 per cent for this age distribution.
(2) All had some pre-existing gynecological disease.
(3) More women of the lower income group ('clinic class').
(4) More Negroes.

Each of the above factors should operate to produce even more cervix cancer in this group than in the average female population. To this extent, therefore, the discrepancy between observed and expected deaths from cervix cancer may be even *greater* than shown by our analysis.

As far as I know, there is no published study in which the question of the prophylactic value of cauterization has been carried as far toward a final definitive answer as yours. The data you have collected are consistent with the hypothesis that cauterization reduces the subsequent incidence of cervix cancer, although it does not provide the final and unequivocal evidence which would be desirable.

I still feel that these results should be made known. I also feel that you should continue this investigation. I would be glad for the opportunity to discuss in greater detail the question of further investigation and analysis of your material."

It must be emphasized that these results were obtained by *deep* cauterization of the cervix, the technique of which was published again in 1941.[3] It is a much more extensive cauterization than is usually done, and the purpose is the destruction of all glands and infected mucosa in the cervix. No aftertreatment is necessary when it is followed by subtotal hysterectomy, but in all other cases, office dilatations with uterine dressing forceps must be carried out to prevent stricture of the cervix. These dilatations are done four, six, eight and ten weeks after operation and again in six months. Anyone who is not willing to carry out these irksome postoperative dilatations should not use this type of cauterization except when hysterectomy is done.

There has been no similar follow-up study of a series of light cauterizations of the cervix so that I am unable to make comparisons as to the relative value of the two procedures in the prevention of cancer. But it is significant that there are no known cases of cancer of the cervix in our own personal series. The two cases that occurred had been cauterized by surgeons when they first adopted this method of cauterization, and one of them volunteered the information that the cervix of his patient was not cauterized to the same extent as is practiced by him now. If chronic infection is a factor in the production of cancer, deep cauterization would seem to be a more logical procedure than superficial cauterization.

It has been stated in the literature that cauterization of the cervix may eliminate cervicitis, but that it could hardly prevent cancer because 80 per cent of cervix cancer develops from the squamous cells of the vaginal portion of the cervix. It is our contention that cancer of the cervix rarely, if ever, develops from normal squamous epithelium but

that it develops at the junction of squamous epithelium and the chronic inflammation of cervicitis either on the surface of the portio or perhaps in metaplasia in the glands, and that if the cervicitis is eliminated, cancer of the cervix will be eliminated practically. Equally fallacious is the argument that cancer of the stump after supravaginal hysterectomy may occur in a normal cervix, based on the fact that the cervix appeared normal at the time of hysterectomy. Masson[4] writes: "It is known that cervicitis is a very common sequel to subtotal hysterectomy. In more than 500 cases, cervicitis with leucorrhea was sufficient to require treatment after subtotal hysterectomy. In many of these cases there was no history of leucorrhea before the body of the uterus was removed." It has been my observation also that a cervix which appears to be normal at the time of hysterectomy may be definitely inflamed on examination months or years later. This is probably the result of circulatory changes, in a glandular structure, which predispose to infection, for if the glandbearing portion of the cervix is excised or destroyed with the cautery as the first step in hysterectomy, no subsequent cervicitis develops.

I will repeat with a few alterations, the following paragraphs of the previous report:

"Perhaps there is no method of preventing cancer of the cervix one hundred per cent, but in our personal series, we have been unable to find a single case and in the entire series of 10,000 cases in two large hospitals, only 2 cases are known to have occurred. A larger series of cases or a longer period of time and a better follow-up may change that report. Even so, if it is shown that the incidence of cancer has been much reduced, the work has been worth while. It is much more satisfactory than a cure of an equal number of cases of cancer of the cervix for many of the cancer cured cases are uncomfortable and unhappy; uncomfortable from undesirable radiation effects, and unhappy because of the dread of recurrence. Our interest has been in the prevention rather than in the cure of cancer of the cervix in the advanced stages in which it is usually seen today.

"Prevention of cancer of the cervix by any method that is effective is advocated in this paper. Deep cauterization has been the method used in this series because it can be done quickly, along with other operative procedures, and microscopic sections show that it is effective in eliminating cervicitis."

Conclusions

1. Chronic cervicitis seems to be a contributing factor in the causation of carcinoma of the cervix.

2. Cancer of the cervix is insidious in onset and because of the late stages in which it is seen today, prevention of cervicitis, prevention of cancer by adequate treatment of existing cervicitis, and early diagnosis by periodic examination of women over 25 years of age, offer the best solution of the problem.

3. In order to destroy infection in the cervix by cauterization, it is often necessary to cauterize deeply and extensively.

4. Careful postoperative care and treatments are necessary to prevent stenosis of the cervical canal after deep cauterization when the uterus is not removed.

5. As far as we know, deep cauterization of the cervix has been an effective method of preventing cancer in our series of 10,000 cases, for only 2 cases of cancer of the cervix are known to have occurred in this series.

6. In the second follow-up study, the average time interval after cauterization was 8.7 years, and the average age of the patient 42.8 years. The results show approximately 80 to 85 per cent reduction in the incidence of cancer, or in deaths from cancer of the cervix in the group followed for by a new application of a statistical method to our series of 4,487 followed patients, Levin estimates the expected incidence as 14 to 23 cases of cancer of the cervix in the time observed. Two cases are known to have occurred before the survey, and one of them died from cancer of the cervix, when 11.6 deaths would be expected.

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AN ANALYSIS OF THE EFFECTS OF CONTINUED THIOUREA TREATMENT IN PREGNANCY AND ON THE DEVELOPMENT OF THE OFFSPRING IN THE RAT*†

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THIOUREA and thiouracil have been used successfully in the treatment of hyperthyroidism in the human.[1-6] Since pregnancy may often be complicated by hyperthyroidism[7] the question as to whether such drugs can be used with impunity to alleviate this condition in the gravid animal becomes an urgent one. Possible effects of the administration of these agents on the fetus and the development of the offspring must also be considered.

The consensus is that these agents act in the manner of a chemical thyroidectomy by preventing the formation of the thyroid hormone.[8, 9] Thyroidectomy in the immature animal has long been known to be followed by a retardation of growth (sheep and goats,[10-11] rabbits,[12] rats[13-15]). More recently Salmon[16, 17] and Scow[18] have reported that removal of the thyroid one to three days after birth results in a marked retardation of growth and maturation of the rat.

We have already reported[19] that thiourea administered to pregnant animals produces a marked hyperplasia of the thyroid glands in the suckling young. Hughes[20] has recently given some information on the effects of thiouracil on the growth of young rats. The present paper furnishes further details concerning the effects on the offspring of thiourea treatment during and after pregnancy.

Methods

At intervals of 0 to 22 days prior to parturition, pregnant rats of an inbred hooded-Wistar strain were placed on a laboratory stock diet containing 0.5 per cent thiourea. Following delivery, all litters were reduced to 6 animals. After weaning from their thiourea-treated mothers, the young rats obtained the drug directly from the thiourea diet. Several of these animals were maintained on this ration for periods of 13 to 157 days, and were then placed on the stock laboratory diet. In several cases, some of the litters were divided immediately after delivery so that some of the young were left with their treated mothers, whereas their litter mates were placed with untreated lactating females.

*Aided by a grant from The Elizabeth Thompson Fund.

†Acknowledgment is made to Mr. Albert Stenger for technical assistance.

Selected animals were sacrificed, the thyroid glands and a number of other organs were weighed rapidly and fixed in Bouin's or Helly-Zenker's solution. Where the thyroids were too small to be dissected without injury, a portion of the trachea with the glands attached was removed and fixed in Bouin's fluid.

TABLE I. EFFECT OF THIOUREA TREATMENT UPON RAT AND THYROID WEIGHT

CASE NO.	AGE DAYS	NO. OF ANIMALS	NO. OF DAYS ON T.T.* PRE-PARTUM	NO. OF DAYS ON T.T.* POST PARTUM	TOTAL DAYS ON T.T.*	STOCK DIET IN DAYS AFTER T.T.	MEAN BODY WT. GM.	MEAN THYROID WT. MG.	MEAN THYROID WT. MG./100 GM. BODY WT.
45-1	21	2	0	21	21	0	30	14	46
45-2	24	3	0	24	24	0	37	19	51
46-1	10	4	0 to 1	10	10 to 11	0	14	5	35
30-1	4	1	4	4	8	0	10	†	--
30-2	8	2	4	8	12	0	17	5	29
30-3	11	2	4	11	15	0	21	7	35
30-4	15	1	4	15	19	0	36.5	10	28
B45	4	2	6	4	10	0	6.5	†	--
47	0	2	7	0	7	0	5	†	--
29-1	1	2	9	1	10	0	5	†	--
29-2	6	2	9	6	15	0	8.5	4	47
29-3	10	2	9	10	19	0	15.5	5	33
41-1	0	3	10	0	10	0	5	†	--
41-2	13	2	10	13	23	0	21.5	6	28
41-3	30	1	10	13	23	17	73	7	9
43-1	0	2	15	0	15	0	4	†	--
43-2	19	2	15	0	15	19	30	4.0	13
43-3	36	2	15	0	15	36	89	9.5	11
38	86	2	22	86	108	0	50	50	100
36-40	222	3	4	157	161	65	200	60	30
36	264	2	4	264	268	0	130	‡	--

*Thiourea treatment.
†Thyroid fixed on trachea.
‡Animals still alive.

Results

Growth.—The feeding of 0.5 per cent thiourea incorporated in the laboratory ration to pregnant rats for 1 to 15 days prior to parturition produced neither visible effects upon the external appearance of the offspring, nor upon the size of the litters. The weights of the newborn from 9 litters of treated animals averaged about 5 grams as did newborn animals delivered by normal untreated mothers.

Continued thiourea treatment via the mother and after weaning through the diet resulted in signs of retardation of growth by the tenth

to the twenty-fifth day of age. The treated rats reached a growth plateau at variable times such as 85, 100, and 157 days of age.

After 157 days on the thiourea diet (Case 36), 4 males averaged 120 Gm., and 2 females 105 grams. The litter was divided so that 2 males averaging 124 Gm. and one 105 Gm. female were left on the experimental diet, and 2 other males averaging 116 Gm. and a female weighing 104 Gm. were placed on the ordinary laboratory ration. Forty days later,

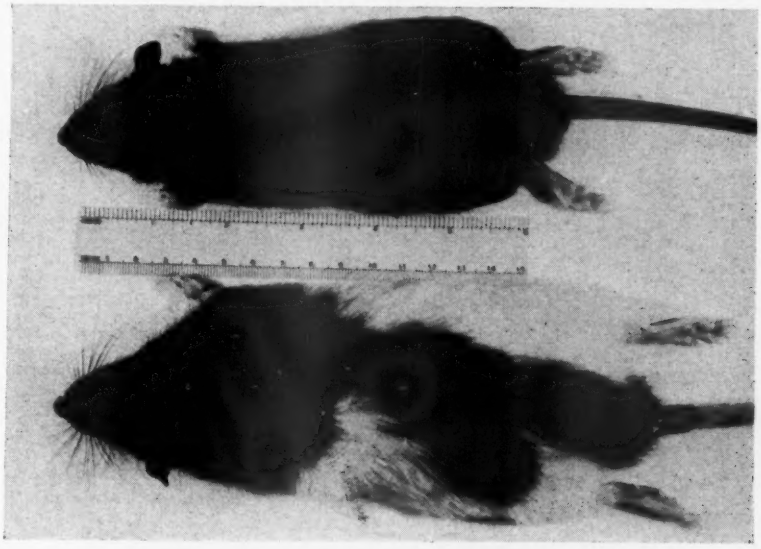

Fig. 1.—Reversibility of thiourea effect (litter mates). Black rat (wt. 125 Gm.) on continuous thiourea treatment for 210 days (4 days prepartum); hooded rat (220 Gm.) on continuous treatment for 161 days and then on normal diet for 49 days.

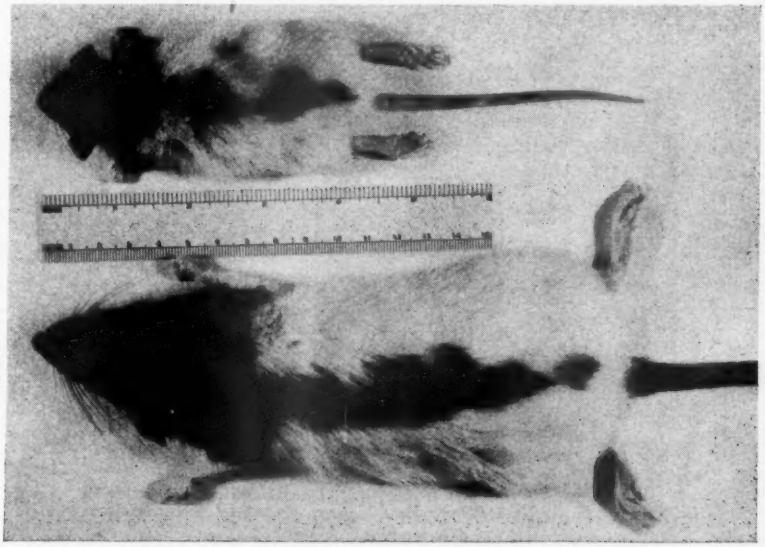

Fig. 2.—Thiourea and growth. 84-day-old thiourea treated animal (50 Gm.) as compared to an untreated animal (160 Gm.) of the same age. The cretin was obtained from a mother treated with thiourea for the entire gestation period.

this latter group showed an average gain of 72 Gm. for the males, and of 41 Gm. for the female. They continued to grow and after 65 days on the normal diet, the males averaged 210 Gm. and the female weighed 180 grams. The males which had been continued on the drug for 55 additional days averaged 126 Gm., and the female remained at 105 grams. The males now 264 days old (107 days since the litter was segregated) average 130 Gm. in weight (Fig. 1).

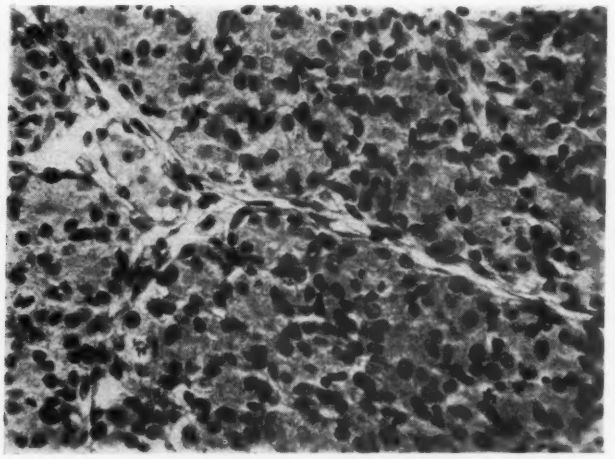

Fig. 3.—One-day-old rat obtained from a mother treated with thiourea for the last 10 days of the gestation period. Note the marked hyperplasia and absence of colloid as compared with that in Fig. 4.

Figs. 3 through 9 are photomicrographs of sections through the thyroid glands of thiourea-treated and normal rats, fixed in Bouin's fluid and stained with hematoxylin and eosin. (×408.)

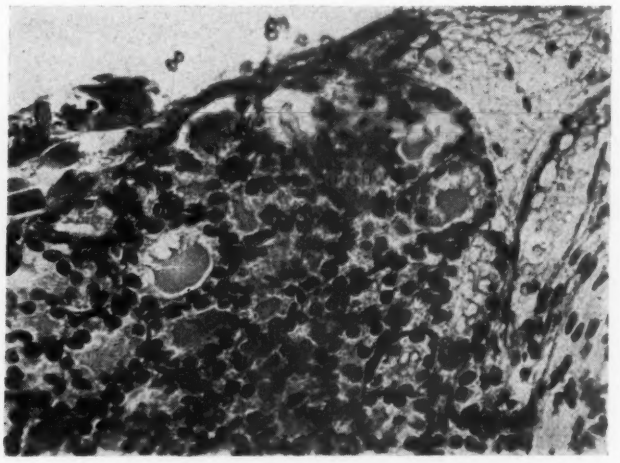

Fig. 4.—One-day-old rat obtained from untreated mother.

In Case 38, a female which had been treated throughout the entire gestation period gave birth to 2 scrawny female young. Treatment was continued and they developed at a greatly retarded rate showing the definite cretin characteristics described by Hughes. At the age of 84

days, one weighed 50 Gm., and the other 78 Gm. (Fig. 2). At this age, our control female rats averaged 160 Gm. and control males, 235 grams.

The Thyroid Glands.—The effectiveness of the pre- and postpartum treatment on the thyroid gland is presented in Table I. The data here disclose that the thyroids of all treated animals range from 28 to 100 mg. of gland per 100 Gm. of body weight. Untreated adult controls of our colony average 8 mg. of thyroid, and our untreated 12 to 18 Gm. animals average 16 mg. of thyroid per 100 Gm. of body weight.

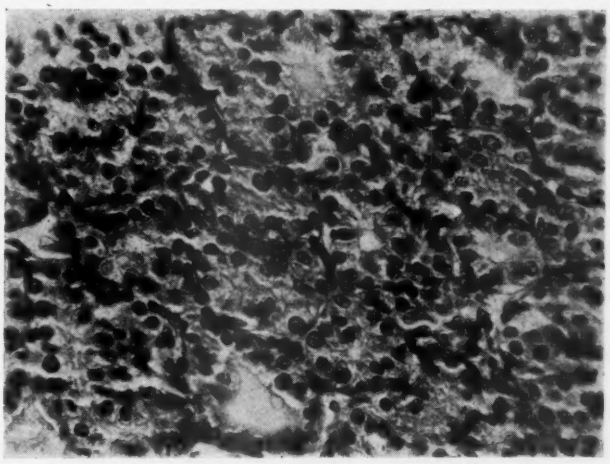

Fig. 5.—Ten-day-old rat obtained from a mother put on a thiourea-containing diet on the day of delivery. Note the higher epithelium and scantier colloid than that in Fig. 6.

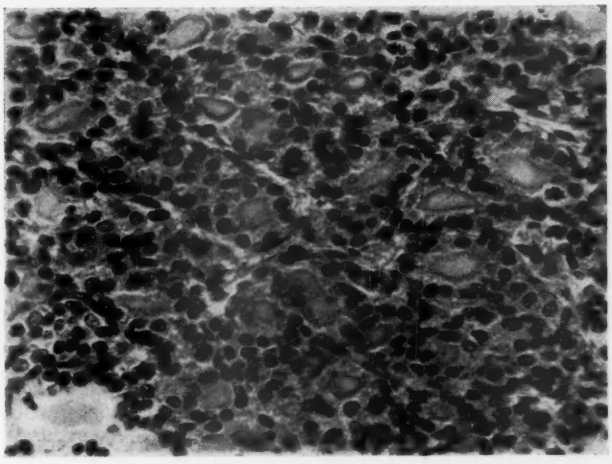

Fig. 6.—Ten-day-old rat obtained from untreated mother.

Several mothers were placed on the thiourea-food 7 (Case 47), 10 (Case 41-1) and 15 (Case 43-1) days prior to parturition. A number of the young were sacrificed at birth, and the glands were fixed attached to the trachea. Macroscopically, the glands appear enlarged and hyperemic. Microscopic examination of the glands reveals some irregularity in the follicles, high columnar epithelium and limited amounts of lightly

staining colloid (Figs. 3 and 4). An histologic study of the thyroids of 10 (Case 46-1) and 21 (Case 45-1) days-old rats nurtured by mothers which had been placed on the thiourea diet on the day of delivery disclose a similar picture (Figs. 5 and 6). Continued treatment resulted in an increase in the weight of the glands as has been established by Mackenzie,[21] Astwood[1] and others.

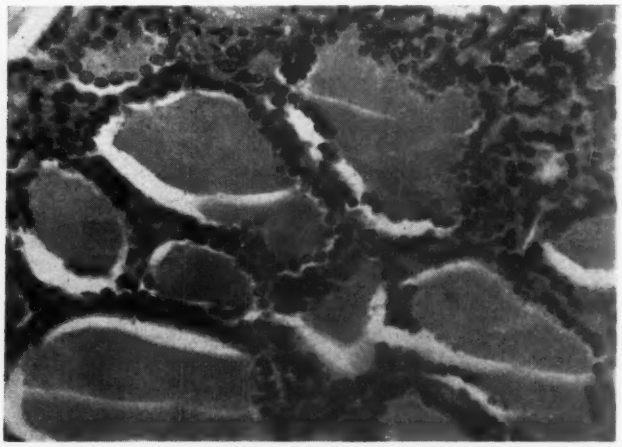

Fig. 7.—Result of thiourea treatment for 161 days followed by normal diet for 65 days. Epithelium is low, approaching the normal picture, and large amounts of densely staining colloid are present.

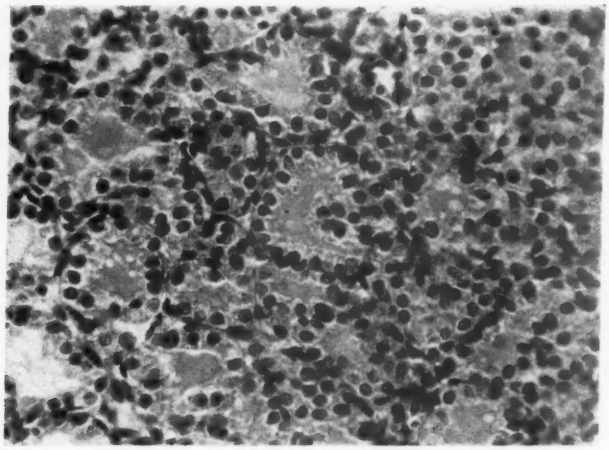

Fig. 8.—Thirteen-day-old litter mate to animal whose thyroid is shown in Fig. 3. Result of ten days of prepartum and 13 days postpartum treatment. The gland is highly active.

It is of interest to note that several rats (Case 36-40) which had been treated for 161 days and then placed on a normal diet for 65 days still possessed large thyroid glands, 30 mg./100 Gm. of rat as compared with 8 mg./100 Gm. for our untreated controls. The histologic picture, however, was that of a normal gland (Fig. 7). Examination of Table I discloses several instances in which short term exposure to thiourea (Case 41-3, 23 days) followed by a return to a normal diet for 17 days

resulted in a reduction in the rate of growth of the gland, and a return to the normal histologic picture (Figs. 8 and 9).

Reproduction.—Mixed litters of our animals maintained on thiourea from the time of birth or prior to it have been observed for 7 months, but none has delivered offspring.

In one instance (Case 39), 6 litter mates (5 females and 1 male) had been kept in one cage on a thiourea ration until they were 100 days old. At this time, the litter was divided and 3 of the females averaging 89 Gm. were transferred to another cage and placed on a stock diet. The male (110 Gm.) and the other female (97 Gm.) were left in the experimental cage. Twenty-one days after being placed on the normal diet, the largest of the females (126 Gm.) delivered 3 healthy young.

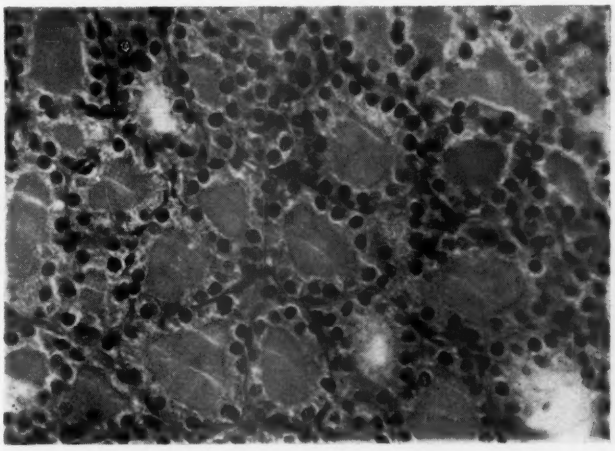

Fig. 9.—Thirty-day-old litter mate to animals whose thyroids are shown in Figs. 3 and 8. Result of return to normal diet for 17 days after a 10-day prepartum and 13-day postpartum treatment. The gland appears normal.

In Case 36, males and females were kept together for 157 days. The litter was divided so that 1 male and 2 females were placed in each cage. Thirty-seven days after being transferred to the normal diet, the 145 Gm. female delivered healthy offspring, and 30 days later external evidences of pregnancy were again visible.

Discussion

The data of the present experiments show that the retarded growth rate and the hyperplastic, activated thyroid glands of young rats, delivered by mothers maintained on a 0.5 per cent thiourea diet during and after pregnancy, were transient in nature. These effects disappeared when the animals were placed on a laboratory stock diet. Administration of the drug in the ration enables one to study the thyroid-developmental mechanism without resorting to surgical thyroidectomy and its attendant hazards. The mortality rate was no higher among our drug-treated rats than among our untreated controls. Hughes[20] has reported a high mortality rate in 25- to 30-day-old animals following daily subcutaneous injections of thiouracil. This difference and the

fact that our animals as a rule were heavier and reached the growth plateau at a later date, may be explained in terms of concentration. Thiourea in a dosage of 0.5 per cent of the diet may have been insufficient to produce cessation of all thyroid hormone production.

The presence of active hyperplastic thyroids in young animals carried by thiourea-fed mothers for 7 to 15 days prior to parturition and sacrificed at birth indicates a definite transplacental transmission of the "thiourea" effect. It is not clear as to how this effect is produced, but 3 possible explanations present themselves. One is the passage of the thiourea (molecular weight, 78) through the placenta. Should this be true, then we have presumptive evidence that the thyroid of the fetus is already a functional gland and on being depressed by thiourea calls upon the pituitary to produce thyrotropin. This would further necessitate the postulation of a functional and active fetal pituitary capable of producing a thyrotropic factor. In support of this, is the finding by Fugo and Witschi[22] that removal of the hypophyseal primordium in the chick embryo results in the development of a small thyroid gland. Fugo[23] concluded further that the embryonic chick pituitary becomes active during the second half of the incubation period and appears to secrete growth, thyrotropic and gonadotropic hormones. Kull[24] has reported that in the albino rat, rapid development of the thyroid gland does not take place until after the eighteenth day in embryonic development, and a fully developed thyroid gland showing follicle and colloid is found only a few hours before birth. The second possibility is that as a result of lowered thyroxine production in the mother, the fetus receives less thyroxine than it would normally, and the pituitary of the fetus responds by sending out increased quantities of thyrotropic factor. The third alternative is that the hyperplasia is brought about by the thyrotropin from the mother.

The last possibility requires that large molecules pass through the placenta from mother to fetus. Ukita[25] claimed that thyroidectomy of pregnant rabbits resulted in the prolongation of gestation, incomplete ossification and hypertrophied thyroids in the offspring. These results may be explained on the possible passage of hypophyseal hormone through the placenta. However, in view of the accepted belief that pituitary tropic factors are protein molecules and the scanty evidence in favor of their transplacental passage, opinion must be reserved.

The sole source of thiourea of animals 45-1 and 46-1 (Table I) was their mothers' milk. The thyroid picture was one of extreme activity. Other animals (Table I) which received both pre- and postpartum treatment showed an increase in size and activity of the thyroid directly related to the duration of treatment. In view of the recent findings by Williams, Kay and Jandorf[26] (cited by Williams, Weinglass, et al.[27]) that human milk contains much more thiouracil than any other body fluid, this result is to be expected.

There is thus presented substantial evidence that in the rat an active hyperplastic thyroid gland may be produced directly through the food containing the drug, and indirectly by transplacental and transmammary passage of the effective factor.

The results disclose that those animals which had been on thiourea for periods up to 157 days, and had reached their growth plateaus resumed growth when returned to a stock diet. The histologic structure of the thyroid also returned to normal. In severe animals treated for 4 days prior to birth and 157 days after birth, the thyroid still weighed 30 mg. per 100 Gm. of body weight 65 days after its return to a normal stock diet. The histology, however, was normal. In the light of Astwood's work[1] and our own in vitro and in vivo studies with adult rats,[28] the return to the normal condition is to be expected.

In rats completely surgically thyroidectomized,[17, 29] repair of the thyroidectomy changes in the pituitary did not occur when thyroid therapy was delayed beyond 40 days. Severinghaus[29] concluded that a rat completely thyroidectomized at birth becomes physiologically hypophysectomized as well. Our own long-term treated rats resumed growth when placed upon a stock diet, indicating that there was no permanent damage of the pituitary.

Although no deliveries were observed in any of the animals while on the thiourea ration, one was inseminated (Case 39) while on thiourea, and gave birth while on the normal food. Williams, et al.[27] have found no abnormalities on the gonads or other organs after thiouracil.

While it is true that the growth of the offspring may be retarded and its thyroid size and histologic activity increased by feeding 0.5 per cent thiourea to the mother, it is clear that no permanent damage has occurred. Although the experimental data gathered from the rodent have been in substantial agreement with those derived from the human being, the results would suggest caution in the employment of thiourea or thiouracil therapy in the treatment of pregnant hyperthyroid females.

Conclusions

1. A supplement of 0.5 per cent thiourea incorporated in the food fed to pregnant rats results in activation and hyperplasia of the thyroid gland, and retarded growth of the offspring.

2. The thiourea effect may be transmitted directly through the food, or indirectly through the placenta, or through the milk.

3. No births were observed in any of the rats while under treatment.

4. A return to a normal diet was marked by a return to normal growth and physiologic activity.

5. Caution in the use of thiourea or thiouracil therapy for cases of pregnancy complicated by hyperthyroidism is advised.

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SQUAMOUS METAPLASIA OF THE CERVIX UTERI

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THE occurrence of squamous epithelium in the cervical canal, which is normally lined by mucus-secreting columnar cells, has intrigued observers for more than 50 years. Added interest in this phenomenon has arisen during the past decades largely because of speculation on the possible relation to carcinoma of the cervix, particularly carcinoma in situ. A number of articles on this aspect of the subject and on differential diagnosis have appeared in the literature;[1-11] the general impression left by these is one of emphasizing the benignancy of squamous metaplasia and deploring mistaken pathologic diagnosis of malignancy. Novak has tersely summed up this majority opinion in discussing a paper by Schmitz and Benjamin:[3] "The so-called metaplasia is clearly benign and here again there is little reason to look on it as having any more influence on the development of cancer than pertains to any chronic irritative lesion." The erroneous diagnosis of malignancy in sections showing only exaggerated metaplasia has undoubtedly been made many times in the past, and conversely, the more grievous error of dismissing preinvasive carcinoma as simple metaplasia has also been committed, though less frequently. That the preinvasive cancers are malignant neoplasms in every sense has been shown by the excellent case studies and follow-up of Smith and Pemberton[8] and Younge.[9] This diagnostic error is declining in frequency as more attention is devoted to the character of the cells and as the old cardinal principle that cancers are necessarily invasive is abandoned.

Another aspect of the subject of squamous metaplasia of the cervix which has received considerable attention is the question of origin of the abnormal cells, and on this topic opinion is divided. The majority of observers seem to agree in whole, or in part, with Meyer[10] who considers metaplasia a step in the healing of erosions. According to his hypothesis, squamous epithelium normally lines the lower portion of the cervical canal in the developing fetus. But as the mucus-secreting cells above begin to function, the squamous cells are destroyed by the macerating effect of the secretion to a line at or near the external os. Subsequently, the lower portion of the canal becomes a kind of battleground between columnar and squamous epitheliums, between the destructive effect of the mucous secretion from above, and the healing growth of squamous cells from below. Undoubtedly, such alternations do occur, but observations on our material suggest that such interplay is exceptional, and we are inclined to agree with Carmichael and Jeaffreson[11, 12] that the atypical

epithelium arises in situ. Similarly, Wollner[4] finds ectopic squamous epithelium only occasionally in extensive erosions where healing would logically be expected.

Meyer's explanation of isolated patches of squamous cells high in the cervical canal as being derived from groups of differentiated basal cells, which were segregated during the fetal adjustment period, is likewise questioned by Carmichael and Jeaffreson.[11] They contend that these basal cells are wholly undifferentiated and are capable of developing toward columnar or squamous epithelium. They find these cells in 95 per cent of human cervices and trace their maturation into fully-developed stratified squamous epithelium. The presence of mucinous material in cytoplasmic vacuoles of squamous-like cells in some involved areas suggests to them the dual potentialities of the basal-cell groups. In the end, the squamous epithelium may assume full adult characteristics, including glycogenation, so that the process is indeed a metaplasia. This line of reasoning is more in keeping with the earlier hypothesis of Ruge[13] and others. Our own observations are confirmatory especially as regards the complete maturation of the metaplastic epithelium. Glycogenation has not been rare in our material, and we have seen an instance of keratinization of the ectopic squamous epithelium in a case of prolapse accompanied by cervical laceration and eversion.

The histologic appearance of the metaplastic epithelium has been fully described in the papers of Carmichael and Jeaffreson[11-12] and has received much attention in this country from various authors. It is beyond our scope to reiterate these observations, but we would like to emphasize two points which we have found to be of value in differential diagnosis: First, the position and morphology of the cells which have been aptly described, especially as regards the outward displacement of the mucus-secreting columnar cells; second, the "festooning" effect which is achieved by the squamous cells in growing over the microscopic undulations of the endocervix. This latter especially pertains to the early phase.

Personal Study

To observe the incidence of squamous metaplasia and to attempt to find some etiologic factors, we have recorded data on a series of over 600 cervices studied for a period of the past four years. The cervices were fixed in toto, and sectioned serially around the external os at intervals of two to three millimeters. From four to ten or more blocks could be cut from each cervix, the number depending on the diameter and outline of the os. Two sections from each block were stained for study, one section being chosen from each face of the block, that is, one "shallow" and one "deep." In this manner, representative samples of the entire cervix were obtained. Blocks of the endometrium and upper levels of the cervical canal were also included with additional sections as indicated in the individual cases.

For convenience 100 consecutive cervices, in which a maximum of satisfactory sections was obtained, were used for statistical analysis. Few significant differences between the figures for the entire series and this sample were noted, and the exceptions are mentioned here. The cervices in sequence which were discarded as unsatisfactory were usually those traumatized incident to surgical removal. Data were recorded on the gross features (laceration, eversion), presence and degree of metaplasia (one to four-plus), location (surface and glandular), evidence of inflammation, and other disease. The clinical data were appended later from the hospital records and in some few cases are incomplete. The results are as follows:

Incidence: Squamous metaplasia was observed in 72 of the 100 cervices in amounts varying from minimal (one-plus) to maximal (four-plus), the latter representing almost complete transformation of the columnar epithelium of the lower cervical canal. This figure is considerably higher than that reported by others. Carmichael and Jeaffreson[12] found an incidence of 41 per cent in their material and 14 of 75 cervices showed metaplastic changes in a series by Schmitz, McJunkin and Macaluso.[6] The percentage is somewhat higher in the studies of cervical polyps. Thus, while Fluhmann[7] found metaplasia in only 59 of 1,195 specimens of cervix with an additional 33 instances of fully-mature squamous epithelium in cervical glands, he found metaplasia in 29 per cent of 100 polyps, and Mezer[15] found it in 31 per cent of 1,636 polyps. The discrepancy between our figure and that of others may be due to differences in methods of examination and differences in interpretation. It was obvious in our material that minute areas of involvement could easily have been missed by anything less than routine serial blocking.

We have not observed a gross feature which would indicate the presence of metaplastic epithelium and have been unable to predict its presence from examination of the fresh specimen. In interpretation, we have freely pronounced as positive the minimal involvement often encountered, but we have not included the basal-cell groups or the occasional upward extension of stratified squamous epithelium from the pars vaginalis over a junctional ulcer.

Race: Race appears to have no effect on the incidence. Of 39 Negroes in the series, 30 or 77 per cent were positive, and of 61 whites, 42 or 69 per cent were positive.

Age: The youngest in the series was 21 and the oldest 51 years. The cases were divided by decades and the results tabulated. (Table I.) We feel that there is a significant increase in incidence from the third through the fifth decades and that this rise is emphasized by a correlated rise in severity. Carmichael and Jeaffreson[12] found an increase of from 35 per cent of cases under 50 years of age to 50 per cent of cases over 50 years, but considered the difference of little import. Our material in the age group over 50 years is insufficient, but the rising incidence by decades seems comparable.

Parity: We find no correlation between parity and the presence of metaplastic epithelium. Seventy-one per cent of the parous (1 to 10) subjects were positive. Of the nine nulliparas, eight or 89 per cent were positive. The one pregnant uterus included in the series was negative. Carmichael and Jeaffreson[12] likewise found no relationship between metaplasia and the number of births.

TABLE I

AGE GROUP	NUMBER	TOTAL METAPLASIA	PER CENT METAPLASIA	PER CENT POSITIVE			
				1-PLUS	2-PLUS	3-PLUS	4-PLUS
21 to 29	22	14	63.5	43.0	35.0	14.0	7.0
30 to 39	47	36	76.6	61.0	19.0	8.0	11.0
40 to 49	20	17	85.0	23.5	23.5	35.0	17.6
50+	5	3	60.0	66.0	33.0		

Menstrual History: This factor also was noncontributory. A wide variety of complaints of menstrual disorders was registered and no relation was evident for anyone. Of the seven women in or past the menopause, five of the cervices (71 per cent) were positive.

Endometrial Phase: Our data for the series are incomplete. Of eight uteri having follicular (proliferative) endometriums, seven or 87 per cent showed squamous metaplasia. Of nine uteri in the progestinal (secretory) phase, four or 44 per cent were positive. However, comparable data for another 100 cervices with endometrial sections showed no appreciable deviation from the "normal" incidence in either phase.

Gross Features of Cervix: Gross appraisal of laceration and eversion was made on the fresh specimen and these were without effect as factors. Of the 58 cervices showing frank tears with ectropion, 42 or 72 per cent were positive. Of those specimens presenting neither, 73 per cent showed metaplasia. This finding is contradictory to the expressed opinion of Meyer[10] and his followers that metaplasia represents a step in the healing of "erosions," and is in keeping with the observations of Wollner[4] as afore-mentioned.

Inflammation: We found it difficult to appraise this item and its possible relationship. Only a rare adult cervix is entirely free from evidence of inflammatory disease if the presence of subepithelial lymphocytes and plasma cells is a reliable criterion of inflammation. However, if the minimal cellular infiltrates be ignored and an arbitrary degree of reaction somewhat denser (two plus in our series) be used as the dividing line, there is suggestive but inconclusive correlation between chronic inflammation and the occurrence of metaplastic epithelium. Thus, the two were observed together in 30 instances, while inflammation without metaplasia was seen in nine cases. These latter include some instances of more acute disease, usually with ulceration, so that the number is probably disproportionately high. Metaplasia without inflammation was observed in 42 cases. Again it is questionable whether the figure is a true index, as there were individual instances in which complete differentiation of the metaplastic epithelium could be interpreted as healing with quiescence of any pre-existing inflammatory disease. Both inflammation and metaplasia were negative in 19 cases.

Other Disease: Under this grouping we have included the accompanying pelvic disorders other than cervical, and in most instances these were the chief clinical and pathological diagnoses. Fibromyomas constituted the most common cause for hysterectomy in the series and occurred in a total of 57 cases, alone in 37, and in combination with salpingitis in 20. Of these 57, 36 or 81 per cent were positive; the presence of salpingitis in combination or its absence was without effect, the figures being 81 per cent and 80 per cent positive, respectively.

The second most frequent complication was salpingitis alone, and six of eleven such cases (54 per cent) were positive. Malpositions of the uterus as a group showed no influence on the incidence (66 per cent

positive); but the three cases of frank prolapse were all positive. Carmichael and Jeaffreson[12] record an incidence of 46.5 per cent in 200 cervices amputated for prolapse as compared with 33 per cent of 134 removed for other reasons.

A wide variety of disorders filled out the remaining cases. Endometriosis occurred three times and all were positive. Single instances of such diverse conditions as congenital malformation and adenocarcinoma of the fundus were included and the findings in the cervix were variable. The one pregnant uterus was negative.

Carcinoma in situ: Preinvasive carcinoma occurred twice in the series. This 2 per cent incidence of cancer is comparable to the figures given by Schiller[16] (3 per cent in one series; 6 in 425 cases in another), but is somewhat lower than that of Wollner[4] (2 cases in 59 cervices). In both of our cases there was metaplasia in addition to the frank neoplasia, but the two processes were entirely distinct. The cancer cells treat the metaplastic epithelium with the same disrespect shown the normal columnar epithelium, uprooting and displacing it from beneath.

Discussion

The individual factors of those examined which appear to exert an influence on the development of metaplasia are age of the patient and inflammation or irritation of the cervix. Age of the patient per se is probably subordinate to age as a factor in ovarian function. The rising curve of incidence of squamous metaplasia from the third through the fifth decades of life roughly parallels the curve of declining ovarian activity with relative hyperestrinism; and from the data of Carmichael and Jeaffreson (our own material being insufficient), this curve appears to continue upward beyond 50 years. The experimental production of uterine metaplasia in various animals[17, 18] by administering large doses of estrogens to castrates is presumptive evidence that a similar process pertains to metaplasia in the human cervix. Indeed, Wollner[4] has described such a human case followed by biopsy while under estrone therapy. The uniform occurrence of metaplasia in the three cases of endometrial hyperplasia in this series lends some support, although admittedly the number is small. Speculation on hyperestrinism as a factor in the production of fibromyomas of the uterus is unwarranted here, but if, as has been suggested, such is possible, endocervical metaplasia in 81 per cent of 57 cases of fibromyomas in this series would be supportive. Against ovarian dysfunction as a factor is the nearly "normal" incidence observed in those individuals having adequate corpus luteum function as judged by the presence of secretory endometrium.

It is our opinion that chronic inflammation plays a more important part in the process than the figures indicate, although its mechanism as a local stimulus is vague. This opinion is based more on the notations of many individual sections than on the series as a whole. We not infrequently remarked on the close anatomic relationship between the two when only one or two of the sections of a given case were positive. It was not uncommon to find isolated patches of metaplastic squamous epitheli-

um accompanied by local round-cell infiltration while the surrounding areas were almost entirely free of both. In the more diffusely involved cervices, the association is not so readily apparent. Nor is association common in the more acutely inflamed lesions, but these are often devoid of all epithelium. In our material, the presence of metaplasia in chronic inflammatory disease seems removed from any function in the healing of erosions, as the ratio in everted and noneverted cervices is almost exact (72 per cent and 73 per cent), and eight of nine nulliparous cervices, grossly free from any lesion, showed varying degrees of metaplasia in the endocervix. Circumferential involvement of the endocervix just proximal to the external os was a fairly frequent observation in nulliparous specimens and in parous specimens in which near perfect healing produced some degree of stenosis. The dilated canal immediately above was usually filled with thick mucus, sometimes inspissated, suggesting that the secretion itself, in the absence of frank infection, may be sufficient stimulus to induce basal-cell proliferation and squamous metaplasia.

Whatever the etiology and significance of the metaplastic epithelium, it seems to bear no relation to malignant disease except for a possible common ancestral cell. We have seen nothing to suggest direct conversion of metaplastic to neoplastic cells. But a common forbear of these otherwise divergent processes does seem a distinct possibility, as has been suggested before.[4] We point out the locus common to both, beginning within the cervical canal and not on the pars vaginalis and the oblique tapering against the normal stratified squamous epithelium at occasional points only in the early stages. In both instances of carcinoma in this series, the neoplasms were removed from the pars vaginalis and occupied positions comparable to the usual location of metaplastic epithelium. Neither involved the whole circumference of the endocervix, nor the whole extent of the surface in any section. The tendency of the cancer cells to grow along natural surfaces, displacing the pre-existing epitheluim, whether columnar or squamous, and to remain in situ for some time suggests a kinship to the metaplastic cells.

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THE RAPID TREATMENT OF EARLY SYPHILIS DURING PREGNANCY

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THE treatment of the prenatal patient with early infectious syphilis has always been a problem. The patient frequently presents herself for the first time so late in pregnancy that it is difficult to give her sufficient treatment. Minor reactions create sufficient inconvenience that the patient fails to receive treatment regularly, while severe reactions necessitate at least a temporary interruption of vital therapy so necessary if the transmission of the disease to the unborn child is to be prevented.

At Bellevue Hospital in December, 1939,[1] we adopted massive arsenotherapy for patients with early infectious syphilis and in 1940, it was decided to give the same type of treatment to prenatal patients with early syphilis. It was felt that intensive therapy would have the advantage of so favorably affecting the patient with early syphilis prior to the fourth month of gestation, that she would not transmit the disease. On the other hand, such therapy given to the infected mother who is further advanced with her pregnancy may appreciably effect a syphilitic infection already transmitted to her offspring.

In 1933, Chargin, Leifer and Hyman successfully shortened the treatment of early syphilis to a period of five days by continuous intravenous drip administrations of neosalvarsan for ten hours daily. Later experiments proved that mapharsen was a much less toxic drug for massive therapy. At Bellevue Hospital, we adopted the rapid massive treatment without using the intravenous drip. The total dosage of mapharsen prescribed was subdivided into equal doses which were given intravenously by syringe at regular intervals for a six- to ten-day period. Since it was found that the administration of more than 1 Gm. of mapharsen in this period was associated with encephalopathy in over one per cent of all patients treated, the total dosage of mapharsen was reduced. Unfortunately, relapses were found to be more frequent in patients who received less than 0.9 Gm. It was then decided to use fever to re-enforce the action of these lowered doses of mapharsen. Various combinations of mapharsen with fever induced by typhoid vaccine were used in order to find a safe and effective plan of treatment.

In these schedules, two injections of about 0.06 Gm. of mapharsen were used on at least one day of treatment.[2] After much experimentation, it was finally decided that the maximum dose of mapharsen given should be approximately 1 mg. per kilogram of body weight, and that only one injection was to be given a day.[3] The average patient would then receive ten daily injections of about 0.06 Gm. of mapharsen. To re-enforce the treatment of this low dosage, four fevers induced by typhoid vaccine were included in the ten days. The fevers were given on the second, fourth, sixth and eighth days. The first fever was induced with an initial injection of 0.1 c.c. triple typhoid vaccine intravenously; the second with 0.2 c.c.; the third with 0.4 c.c., and the last with 0.6 cubic centimeters. From two to three hours after the initial injection, another dose of equal amount was given in most cases. In general, a fever of at least 104° F. for about four hours was obtained. In June, 1943, we added bismuth to our schedule of rapid treatment, giving 0.1 Gm. of bismuth salicylate in oil on the first, third, seventh and tenth days of therapy. Thus, our standard plan of therapy came to be as follows:

TREATMENT	DAYS									
	1	2	3	4	5	6	7	8	9	10
Mapharsen—1 mg. per kilogram	x	x	x	x	x	x	x	x	x	x
Bismuth salicylate in oil—100 mg.	x		x				x			x
Typhoid vaccine in c.c.		0.1		0.2		0.4		0.6		
		0.1		0.2		0.4		0.6		

Choice and Preparation of Patients

The plan of therapy for the treatment of syphilis in the nonpregnant acted as a proving ground before carrying out a similar procedure in the pregnant patient. With a few exceptions, cases with early syphilis were chosen first since the obvious effects of therapy could be more readily appraised in these cases. Thus, there were 36 pregnant patients with early infectious syphilis: two with seronegative primary syphilis, three with seropositive primary syphilis, 28 with secondary syphilis and three with relapsing secondary syphilis. In this group the syphilitic lesions appeared in 16 during the first trimester, in 13 during the second, and in seven during the last trimester. In addition, five patients with early latent syphilis and two with late latent syphilis were treated. Intensive treatment was given anytime during the course of pregnancy depending upon the time the patient presented herself. Contraindications to such intensive therapy include active tuberculosis, nephritis, decompensated heart disease, toxemias of pregnancy and any chronic hepatic disease. No such contraindications were present in any of this group.

All patients were subjected to a complete physical examination to rule out any medical or obstetrical contraindication to intensive therapy. Blood pressure, urine examinations and blood counts were taken before treatment was started and frequently throughout the course of therapy. Cisternal punctures were performed on about half of the cases with no resulting harmful effects.

Reactions to Intensive Therapy in General

In the nonpregnant patients, encephalopathy was practically the only severe reaction occurring with intensive therapy. Among 321 treatment courses with mapharsen alone, in a six- to ten-day period, the incidence of encephalopathy was 1.6 per cent.[3] In a subsequent series of 588 treatment courses with combined fever and mapharsen where two injections of about 0.06 Gm. of mapharsen were given on at least one day of treatment, the incidence of encephalopathy was 1.36 per cent.[3] In the total series of 909 treatment courses, the mortality rate from encephalorrhagia was one in 300, a mortality rate much too high to justify this plan of therapy. With the subsequently employed ten-day plan of treatment previously outlined, 1,303 treatment courses were given, the incidence of encephalopathy being 0.3 per cent with a mortality rate of 1 in 1,303. In the total group of 2,212 patients treated, several other reactions were noted. One patient developed a mild arsenical dermatitis. There were 100 instances of early acute arsenical erythemas and urticarias. In addition, mild transient jaundice occurred in five patients, in three during hospitalization, in 1 three weeks, and in 1 six months after therapy. There were four instances of transient hematuria noted in those patients receiving mapharsen and fever therapy. Also, one patient developed agranulocytosis and recovered completely. Mild peripheral neuritis was noted in five instances. Nausea and vomiting occurred with great frequency following the first few injections of mapharsen. In very few instances did this persist with subsequent injections, and never did this reaction warrant discontinuation of therapy. Concomitantly with fever, practically all patients complained of headache and malaise. When these latter symptoms are severe they may be relieved by sedatives, the choice being morphine.

Types of Treatment and Reactions With Intensive Therapy During Pregnancy

Forty-three pregnant patients were treated. Six cases of secondary syphilis were treated with mapharsen alone: one patient received 1.2 Gm. mapharsen in six days, one received 0.88 Gm. in nine days, three 0.84 Gm. in six days, and one patient 0.72 Gm. in six days, depending upon the dosage in vogue at the time. Eight patients received from 0.6 to 0.8 Gm. of mapharsen and two to three fevers in seven to eight days. Twenty-nine patients were placed on the ten-day plan of treatment finally adopted with 0.5 to 0.6 Gm. of mapharsen and three to four fevers in the ten-day period. Twenty-three of these patients also received bismuth.

In this pregnant group, vomiting frequently followed the first few injections of mapharsen. In only one instance did a patient continue vomiting throughout the entire course of mapharsen therapy. With fever induced by typhoid vaccine, subcutaneous injections of morphine sulfate were given to the pregnant patients who complained of vomiting, headaches, generalized aches and pains with marked relief. One patient had a ninth day erythema of Milian. In three patients nose bleeds were encountered. There were no instances of jaundice, agranulocytosis, or peripheral neuritis. Unfortunately, the last patient treated developed arsenical encephalopathy and died following the fifth injection of 0.07 Gm. of mapharsen with one previous fever episode. (This is the single fatality noted in the total 1,303 courses of treatment previously mentioned.)

Three patients complained of mild abdominal cramps during their first episode of fever. These abdominal cramps were not associated with obvious uterine contractions. One of these three patients as well as another who was free from abdominal pain, had a slight bloody vaginal discharge on the day following fever therapy. This discharge lasted for a few hours and then subsided. Further mapharsen therapy as well as typhoid vaccine was continued without a recurrence. One patient who was admitted with early syphilis, vaginal bleeding and abdominal cramps withstood mapharsen and fever therapy without any recurrence of bleeding or abdominal pain.

Twenty-six of the 29 patients who were placed on the ten-day plan of therapy completed this treatment. Of the three patients who did not complete their course of treatment, one was the patient who died of arsenical encephalopathy; one was a patient with secondary syphilis who was four and one-half months pregnant, and delivered a stillborn fetus on the second day of treatment having had two injections of mapharsen and one fever; the third was a patient with late latent syphilis who was six months pregnant, and delivered a stillborn fetus after 0.42 Gm. of mapharsen and three fevers. The last patient gave a history of having had six spontaneous abortions, several before and several after she had acquired syphilis.

Results of Treatment of Pregnant Patients With Early Infectious Syphilis

The results of treatment in the mothers and babies are classified according to the type of intensive therapy given, i.e., mapharsen alone, the seven- to eight-day plan of treatment with mapharsen and fever, and the finally adopted ten-day plan with mapharsen, bismuth and fever.

Six patients with secondary syphilis were treated with mapharsen alone. (Table.) Two patients who were treated in the second trimester relapsed shortly before delivery with the result that one patient (V. M.) delivered a premature macerated stillbirth, and the other (J. S.) a full-term baby who developed secondary syphilis two weeks after birth. The other four patients delivered babies who were apparently free from syphilis. One of these children was seropositive at birth and had negative serologic tests for syphilis (hereafter abbreviated as STS) at three, six and nine months of age. One baby was not examined at birth but had negative STS at five months of age. The other two were seronegative at birth; one having negative STS at eight months of age and the other lost to subsequent follow-up. Of the mothers who delivered, the four apparently healthy babies, one had negative STS and 3 positive STS at the time of delivery.

In the second group (Table II), eight patients with primary, secondary or relapsing secondary syphilis received 0.6 to 0.8 Gm. of mapharsen and two to three fevers induced by typhoid vaccine. One patient (A. B.) at thirty-seven weeks delivered a macerated fetus; the mother's STS was positive at the time of delivery. The other seven patients delivered apparently healthy babies, six at term and one close to term. The seventh day STS were negative in six of the babies and positive in one of the babies. The last baby had positive STS two and one-half months after birth, but completely negative STS, three, four and seven months after birth. Two have not been seen since birth, and the other four had negative STS when examined at three to twenty-four months of age. In

TABLE I. THERAPEUTIC RESULTS IN PATIENTS TREATED WITH MAPHARSEN ONLY

PATIENT	LENGTH OF PREGNANCY AT ONSET OF TREATMENT	MOTHER'S INTRA-PARTUM STS*	TERM OR PREMATURE	BABY'S CONDITION	BABY'S 7TH DAY STS	FOLLOW-UP STS OF BABY	FOLLOW-UP OF MOTHER
V. M.	5 months	Strongly positive	32 weeks	Macerated	--	--	Relapsed before delivery.
J. S.	6 months	Strongly positive	Term	Good	Positive	Secondary syphilis 2 weeks after delivery	Relapsed before delivery.
M. C.	5½ months	Negative	Term	Good	Negative	Negative at 1 and 8 months	Negative 18 months after treatment. Spinal fluid normal.
E. T.	4½ months	Strongly positive	28 weeks	Good	No report	Negative at 5 months	Positive 4 years after treatment. Spinal fluid normal.
E. N.	8 months	Strongly positive	Term	Good	Positive	Positive 1 month; negative 3, 6 and at 9 months	Negative 27 months after treatment. Spinal fluid normal.
C. N.	7½ months	Positive	Term	Good	Negative	Lost	Lost.

*STS = serologic tests for syphilis.

TABLE II. THERAPEUTIC RESULTS IN PATIENTS TREATED IN 7 TO 8 DAYS WITH 0.6 TO 0.8 GM. OF MAPHARSEN AND 2 TO 3 FEVERS INDUCED BY TYPHOID VACCINE

PATIENT	LENGTH OF PREGNANCY AT ONSET OF TREATMENT	MOTHER'S INTRA-PARTUM STS*	TERM OR PREMATURE	BABY'S CONDITION AT BIRTH	BABY'S 7TH DAY STS	FOLLOW-UP STS OF BABY	FOLLOW-UP OF MOTHER
A. B.	4½ months	Positive	37 weeks	Macerated	--	--	Lost.
L. W.	3½ months	Positive	Term	Good	Negative	Negative at 6 weeks and at 6 months	Negative 23 months after treatment. Spinal fluid normal.
E. M.	8½ months	Strongly positive	Term	Good	Negative	Negative at 3 months	Negative 5 months after treatment.
D. D.	6½ months	Positive	Term	Good	Negative	Negative at 2 and 5 months	Negative 9 months after treatment.
A. C.	5 weeks	Negative	36 weeks	Good	Negative	Negative at 3 and 24 months	Negative 30 months after treatment. Spinal fluid normal.
M. B.	2 months	Negative	Term	Good	Negative	Lost	Lost.
E. S.	4½ months	Negative	Term	Good	Negative	Lost	Negative 11 months after treatment.
M. L.	8 months	Strongly positive	Term	Good	Positive	Positive at 1 and 2½ months. Negative at 3, 4 and 7 months	Negative 15 months after treatment. Spinal fluid normal.

*STS = serologic tests for syphilis.

TABLE III. THERAPEUTIC RESULTS IN PATIENTS TREATED IN 10 DAYS WITH 0.6 GM. MAPHARSEN AND FOUR FEVERS INDUCED BY TYPHOID VACCINE

PATIENT	LENGTH OF PREGNANCY AT ONSET OF TREATMENT	MOTHER'S INTRA-PARTUM STS*	TERM OR PREMATURE	BABY'S CONDITION AT BIRTH	BABY'S 7TH DAY STS	FOLLOW-UP STS OF BABY	FOLLOW-UP OF MOTHER
L. N.	2 months	Positive	16 weeks	4 mo. fetus	--	--	Negative 10 months after treatment.
F. B.	3 months	Positive	29 weeks	Good	Positive	Died 6 days after birth	Positive 6 months after treatment. Spinal fluid normal.
M. B.	6 months	Positive	Term	Good	Positive	Too early	Too early.
B. W.	8½ months	Positive	Term	Good	Positive	Too early	Too early.
L. W.	6 months	Positive	Term	Good	Positive	Negative at 3 months	Negative at 3 months.
R. W.	3 months	Negative	Term	Good	Negative	Negative at 5 months	Negative 14 months after treatment.
B. E.	7 months	Positive	Term	Good	Negative	Negative at 2, 4, 7 and 12 months	Negative 12 months after treatment. Spinal fluid normal.
F. S.	4 months	Positive	32 weeks	Good	Negative	Negative at 2 months	Negative at 11 months. Spinal fluid normal.
R. W.	2 months	Negative	Term	Good	Negative	Negative at 1 month	Negative 7 months after treatment.
E. D.	6 months	Negative	Term	Good	Negative	Negative at 4 months	Negative 5 months after treatment.
T. J.	4½ months	Negative	Term	Good	Negative	Lost	Negative 6 months after treatment.
A. G.	2 weeks	Negative	Term	Good	Negative	Lost	Negative 9 months after treatment.
J. S.	2½ months	Negative	Term	Good	Negative	Lost	Negative 7 months after treatment.
R. L.	5 months	Negative	Term	Good	Negative	Lost	Negative 4 months after treatment.
R. H.	2 months	Negative	Term	Good	Negative	Too early	Negative 7 months after treatment.
N. C.	7 months	Positive	Term	Good	Negative	Lost	Positive 2 months after treatment.

*STS = serologic tests for syphilis.

summary, of the eight babies delivered, there were seven apparently healthy babies and one premature macerated stillbirth. Of the mothers who delivered the apparently healthy babies, three were seronegative, and four were seropositive at the time of delivery.

In the third group, 21 patients with early infectious syphilis were placed on the finally adopted ten-day plan of therapy. Of these, three have been lost from observation, and two have not delivered as yet. Therefore, the discussion of the results of this group is confined to 16 patients (Table III). One patient (L. N.) had a spontaneous abortion in the fourth month of pregnancy, two months after completion of treatment. Although her STS were positive at the time of abortion, she received no further treatment and eight months later her STS became negative. One premature baby (F. B.) of twenty-nine weeks' gestation who was seropositive at birth, died six days after delivery. The other 14 patients delivered apparently healthy babies, one premature and 13 at term. Three of these babies were seropositive and 11 seronegative at birth. Two of the seropositive babies were delivered so recently that further STS have not been done as yet. The third baby who was seropositive at birth, now has negative STS at three months of age. Of the 11 babies who were seronegative at birth, five were followed and were negative at one to twelve months of age, while six have not had STS since birth. In summary, of the 16 babies delivered, there were 14 live infants, 12 of whom have negative serologic tests, and two with seropositive tests at birth who have not been rechecked. There were two failures. Of the 14 mothers who delivered live infants, six were seropositive and eight seronegative at the time of delivery.

Analysis of Results

Combining the results of the three plans of therapy we find that of the 30 babies delivered, 23 have seronegative reactions, 14 having been followed one to twenty-four months. Seven have been classified as failures; the two premature macerated fetuses, the four-month stillborn fetus, the premature child who died 6 days after birth, the child who developed secondary syphilis, and the two recently born children who were seropositive at birth and have not been rechecked. The last two while included among the failures may subsequently prove to have negative STS as did three other babies, who while seropositive at birth, became seronegative at three months of age. The mother who aborted the four-month fetus was seronegative eight months later, and it is very possible that the abortion was not due to her syphilitic infection.

Since it is admittedly infrequent for a child born with negative STS to develop a positive reaction at a later date, the nine children seronegative at birth but subsequently lost to follow-up have been included among the probable good results with the 14 who were followed for longer periods. The probable good results (23 out of 30) would then be at least 76.6 per cent.

Relationship of the Onset of Treatment to the Length of Gestation

In the routine treatment of syphilis in pregnancy, a direct relationship can be observed in the results obtained and the time in pregnancy that treatment was started.[4] No such relationship is apparent in the intensively treated cases. Of the nine mothers who were treated in the first trimester of pregnancy, seven babies have been classified as good

results, and of the 13 who were treated in the second trimester, nine delivered babies free from syphilis. Eight mothers were treated in the third trimester and seven of their babies were healthy.

Intensive Treatment of Latent Syphilis During Pregnancy

While no effort was made to obtain a series of intensively treated latent syphilitic prenatal patients, seven pregnant women with latent syphilis were given this type of therapy because it was felt that they were too unreliable for the orthodox plan of treatment. Of these seven, three had syphilis of less than six months' duration. One of these was the girl who died from arsenical encephalopathy, one has been lost from observation and one has not delivered as yet. Four patients had syphilis of unknown duration. Of these, two had babies with negative STS at birth and two months after birth. One who was six months pregnant delivered a stillborn fetus in the middle of her treatment, and one patient has not delivered as yet. Obviously, no conclusion can be drawn from this small series of cases.

Results of Therapy in Patients Who Became Pregnant After Previously Receiving Intensive Therapy for Early Syphilis

Most authorities agree that all pregnant women who have or have had syphilis should be treated with each pregnancy irrespective of previous therapy, or the status of their serologic tests. We wished to learn whether it was necessary to treat patients who had received massive arsenotherapy prior to pregnancy.

After a patient finished the rapid treatment, no further therapy was given unless a relapse occurred. Thirty-two of our intensively treated patients subsequently became pregnant and received no further treatment during their pregnancy. Two had previously been treated for early latent syphilis, and 30 for secondary syphilis. Of these 32 patients, 27 delivered healthy babies, 26 at term and one after 30 weeks of gestation. Five had spontaneous abortions of which only one was due to syphilis. Of the twenty-seven who had healthy babies, four delivered ten to eleven months after antisyphilitic treatment, eight delivered twelve to seventeen months, five delivered eighteen to twenty-three months, and 10 delivered twenty-four months after their intensive therapy. Twenty-five mothers had negative intrapartum serologic tests for syphilis. All of these had seronegative babies. Two mothers had positive intrapartum serologic tests for syphilis; one baby was seronegative at birth and one was seropositive, but became seronegative within one month. Three of these patients became pregnant a second time subsequent to previous intensive treatment and these babies had negative serologic tests for syphilis.

In this group of previously intensively treated patients, five patients had spontaneous abortions. One became pregnant three months after treatment. At the onset of her pregnancy her serologic tests for syphilis were slightly positive. She aborted at the end of three months at which time her STS were negative. She has been followed for forty-seven months since then, and has had negative STS as well as a normal spinal fluid. Another patient had negative STS four months after treatment. She became pregnant one year after treatment and aborted after two months. For three months following the abortion, she has had consistently negative STS and normal spinal fluid findings. A third patient became pregnant two months after completion of treatment and

aborted at the end of three months. Her STS were slightly positive at the time of her abortion, but became completely negative during the next two months. A fourth patient who had negative STS at the onset of her pregnancy four months after previous intensive treatment subsequently delivered a six-month fetus which died one hour after birth. The mother was followed for twenty-seven months during which time she had negative STS and normal spinal fluid findings. A fifth patient who conceived soon after completing her intensive therapy delivered a six-month macerated fetus at another hospital. She was seen by us one month later, at which time she had secondary syphilis with dark-field positive lesions.

Thus, of the 32 patients, five aborted and 27 had normal babies one being premature. In only one instance of the five early terminations can syphilis be held responsible.

Comparison of Therapeutic Results and Reactions of Massive Arsenotherapy With Routine Treatment

Prior to the advent of intensive therapy, the records of the prenatal syphilis clinic at Bellevue Hospital, since 1936, reveal that 34 patients with early infectious syphilis received routine treatment during their pregnancy. Of these 34, one died from arsenical encephalopathy and one was lost from observation. Of the remaining 32 patients, five delivered macerated stillbirths and 11 delivered syphilitic live babies, two of whom died a few weeks after birth while under therapy. Sixteen babies were apparently free from syphilis, having negative STS from seven days to two years after birth. The probable satisfactory results under this plan of therapy are 50 per cent as compared to the minimum of 76.6 per cent obtained by massive arsenotherapy. The poor results of the routine type of therapy are due to the inadequate, irregular treatment received by these patients. The inadequacy of treatment is due to the limited time available with routine treatment to give the patient a sufficient amount of the arsenical drugs. Only four received more than ten injections of arsenical drugs before the termination of pregnancy. Among 23 prenatal patients with early infectious syphilis who received no antisyphilitic therapy, no baby escaped syphilis. As a result of the superiority of intensive therapy as compared to routine therapy, there is a diminishing incidence of prematurity and maceration as well as live syphilitic babies. Table IV shows the comparative results in the three groups.

TABLE IV. COMPARISON OF RESULTS OF TREATMENT OF PREGNANT PATIENTS WITH EARLY INFECTIOUS SYPHILIS

TYPE OF TREATMENT	TOTAL NUMBER FOLLOWED	PREMATURE	MACERATED	NUMBER OF NEONATAL DEATHS DUE TO SYPHILIS	LIVE SYPHILITIC BABIES UNDER TREATMENT	BABIES APPARENTLY FREE FROM SYPHILIS
Massive arsenotherapy	30	7*	2	1	1	23 (76.6%)
Routine treatment	32	10†	5	2	9	16 (50%)
No treatment	23	14	6	5	12	0 (0%)

*Two of these premature babies were free from syphilis.
†Three of these premature babies were free from syphilis.

Of the 34 patients given routine treatment for early infectious syphilis, three were treated with mapharsen, 8 with arsphenamine and 23

with neoarsphenamine. A study of the reactions encountered in this group revealed one death due to arsenical encephalopathy after two injections of neoarsphenamine (0.2 and 0.3 Gm.), five cases of jaundice (four from neoarsphenamine), and one case of exfoliative dermatitis after neoarsphenamine. In the group of 43 prenatal patients who received massive mapharsen therapy, one death occurred from arsenical encephalopathy, the onset of this complication developing after the fifth mapharsen injection, and there were no cases of jaundice or exfoliative dermatitis.

Discussion

From the data given, the rapid treatment of early syphilis in pregnant women has given encouraging results. In a group of 30 prenatal patients with early infectious syphilis who completed treatment, we have classified seven as failures. However, not all of these babies are definitely syphilitic. Two babies who were seropositive at birth had been delivered too recently for re-examination. These babies at a later date may prove to be seronegative. In the case of the four-month stillborn fetus, the mother became seronegative subsequently without further treatment. No autopsy was obtained in this case. It is extremely unlikely for syphilis to produce abortion prior to the fourth month of gestation and therefore, it is questionable whether this poor result was due to a syphilitic infection. In view of the uncertain status of these three cases, if they were to be deducted from the series, there remains four poor results ascribable to syphilis out of a total of 27 cases, a corrected salvage rate of 85 per cent. Based upon the same assumptions, the results with the various plans of rapid therapy are as follows: Of the six patients treated with mapharsen alone, probable good results were obtained in four (66 per cent); of eight patients treated with the seven-day plan of combined mapharsen and fever therapy, there were seven good results (87 per cent); of the 13 patients treated with the ten-day plan of combined mapharsen, bismuth and fever, there were 12 good results (92 per cent).

More severe reactions were encountered in the prenatal patients with the routine plan of therapy than were found with the intensive plan of therapy. However, the routine plan of treatment consisted chiefly of the administration of arsphenamine and neoarsphenamine. Admittedly, the reactions with these drugs are greater than with mapharsen. It is well established that pregnant women have an increased susceptibility to arsenical drugs with resulting reactions particularly encephalopathy. One death from this cause resulted after only five injections of mapharsen in the rapid plan of treatment, and one death occurred from 2 small doses of neoarsphenamine in the routine plan of therapy. This emphasizes the need for caution in the use of arsenical drugs when treating syphilis in pregnancy. It must be recognized, however, that from the foregoing data massive mapharsen therapy combined with fever and bismuth has proved less toxic than the older forms of routine therapy.

Conclusions

1. Forty-three pregnant patients were treated for syphilis with massive mapharsen therapy. One death from arsenical encephalopathy occurred in this group. Of the 30 patients with early infectious syphilis who completed treatment and were kept under observation, good results from this therapy were obtained in a minimum of 76.6 per cent. If the babies not proved to be syphilitic are eliminated from the calculations, the probable good results would be 85 per cent.

2. At the Bellevue Hospital prenatal syphilis clinic between 1936 to 1940, prior to the advent of massive arsenotherapy, there were 34 pregnant patients treated for early infectious syphilis with routine therapy. One death occurred from arsenical encephalopathy, five patients developed jaundice and one exfoliative dermatitis. Only 50 per cent of the offspring were free from syphilis.

3. In the relatively small series reported here, intensive therapy proved safer and more effective than routine treatment. Nevertheless, there remains the risk of arsenical encephalopathy and this is probably greater with intensive mapharsen therapy than when the same drug is employed in routine treatment.

4. Massive mapharsen therapy in the treatment of early infectious syphilis prior to the onset of pregnancy has yielded excellent results, since there was only one failure among 32 patients so treated. This failure occurred in a mother who had a cutaneous relapse.

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NEISSERIAN INFECTION IN PREGNANCY*

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Introduction

AN EARLIER and confusing experience with smear and culture in the diagnosis and management of gonorrheal infection complicating pregnancy prompted the present study. The first observation was confined to antepartum patients in a Prenatal Clinic for expectant mothers of low income, who had relatively good social standards. A medical technician trained in the interpretation of smear and cultural procedures, the necessary laboratory facilities, and an experienced venereal disease contact investigator were accessible. From the beginning, it was apparent that certain patients had repeated positive smears, negative cultures, and sexual partners with no evidence of infection as shown by negative smears, cultures, and clinical findings. It was likewise noted that patients with positive cultures, usually had positive smears, clinical evidence of infection, and their contacts had gonorrhea. These disconcerting findings caused suspicion as to the effectiveness of smear alone in the diagnosis of gonorrhea, and increased the responsibility of making a correct disposition of the cases. It appeared unjust to stigmatize the expectant mother with a diagnosis of gonorrhea and subject her to the marital discord which resulted when she informed her husband that she was not only pregnant but had gonorrhea, when neither had little if any evidence of infection. The problem was further magnified by the seemingly unnecessary cost of treatment and delivery, when the hospital isolation rules required a private room and special nurses for both mother and infant, if smear from the urethra of mother or eyes of infant was positive.

This study was planned in an attempt to clarify some of the problems encountered in the antepartum patients, namely: How efficient is smear compared to culture in the diagnosis of gonorrhea? Can the gonococcus be transmitted from the antepartum to the postpartum state and if so how? Is it activated by the trauma of labor, and if so can it be found in the intrapartum and postpartum discharges from the vagina? When is the patient free of gonococci following treatment? How frequently is the gonococcus the cause of postpartum morbidity? Is the diagnosis more confusing in the pregnant than in the nonpregnant patient?

*Thesis submitted to the faculty of the Graduate School of Medicine of the University of Pennsylvania, toward the requirements of the degree of Master of Medical Science (M. Sc. [Med.]) for graduate work in obstetrics and gynecology.

Theory

Whereas, the first observation was confined to the antepartum period, this study was extended into the intrapartum and postpartum periods. It was predicated on the belief that chronic gonorrheal infection localizes in the deep urethral tissues, adjacent glands and ducts, Bartholin glands and ducts, and in the cervical glands;[1] and that the gonococcus may be pressed out of the deep cervical glands,[2] and expelled in the mucous plug which may contain a large part of the proliferated cervical mucosa,[2, 3] and may be activated by the traumatizing effect of labor,[2] and found later in the show and lochia and recovered by culture. It is recognized that trauma of instrumentation materially exaggerates a latent infection, and the passage of an instrument into the urethra to stir up a latent focus of infection is considered most useful[4] by the male urologist. Therefore, one might expect a higher incidence of morbidity, with clinical evidence of disease and gonococci in the discharges of parturient patients harboring gonorrheal infection, whose glandular structures have experienced such a marked degree of trauma.

Method

Urethral and cervical smears and cultures were taken on all patients admitted to the Prenatal Clinic. Urethral smears were taken on all patients admitted to the hospital in labor and checked with culture if positive, suspicious, or patient had clinical evidence of infection. The smear and culture were taken at the same time in as many patients as possible. A specimen of show was taken at or near complete cervical dilatation, and urethral and lochial cultures were taken on about the first, third, fifth, and seventh postpartum days. The cultures of show and lochia were taken from the vagina by separating the labia and inserting a sterile applicator for a distance of 2 centimeters. The vagina was not invaded to examine the cervix after the seventh month of pregnancy, unless under aseptic precautions in the hosptial, and in each instance was for other obstetric complications, i.e., ruptured membranes, bleeding, etc., gonorrheal infection not being suspected. Two culture methods were employed,[5*] but *Neisseriae* were reported positive only following a positive oxidase reaction, the presence of typical gram-negative diplococci from an oxidase positive colony, and typical sugar fermentation reactions. Smears were considered positive if gram-negative intracellular diplococci resembling the gonococcus were present. Patients were discharged from the hospital to the clinic, if urethral and cervical cultures were negative on three alternate days, beginning three days after termination of treatment. All patients were treated and followed for cure while isolated in the hosptial, and were referred back for further treatment, if found to harbor organisms while under observation in the clinic.

*The specimen was collected on a sterile swab which was placed in 2 c.c. of sterile broth (2 per cent Difco proteose peptone No. 3 and 0.5 per cent NaCl) and distributed well in the tube. Chocolate agar (Difco Bacto-proteose No. 3 and Bacto-hemoglobin) was inoculated with the above suspension and was then smeared over the surface of the plate. Plates were incubated at 35 to 37 degrees Centigrade for 48 hours, in a chamber providing increased moisture and an atmosphere of 8 to 10 per cent carbon dioxide.

Fifty obstetric patients have been proved to harbor *Neisseriae* by cultural identification, and are presented with forty-four patients who had findings suggesting gonorrhea infection and/or positive smears, in an attempt to clarify certain problems encountered in the management of gonorrheal infection in pregnancy.

Duration and Condition of Pregnancy at the Time of Diagnosis

Seven patients were admitted as abortions, four being threatened, two complete, and one incomplete. Thirty-five patients had normal intrauterine pregnancies with one being in the first trimester, eleven in the second trimester, and twenty-three in the third trimester. Three of the patients in the third trimester were admitted because of bleeding. Eight patients were diagnosed postpartum following term delivery. The average time of delivery was 34 weeks for all cases. Nineteen patients gave a history suggesting gonorrhea, and thirty-one patients denied knowledge of previous infection. Thirty-four patients enumerated suspicious symptoms, and sixteen patients denied symptoms. Forty-four patients had suggestive clinical findings, and six patients showed no evidence of urogenital infection.

Comparative Efficiency of Smear and Culture

The urethral smear was positive in 62 per cent, and the cervical smear positive in 73.3 per cent of patients. Thirty patients had both urethral and cervical smears, and each was positive in 69.5 per cent, and each was negative in 30.5 per cent of this group. The urethral culture was positive in 75 per cent, and the cervical culture was positive in 87.5 per cent of cases. Thirty patients had both urethral and cervical cultures, and both were positive in 46.6 per cent of cases.

Culture Control Group

Ten patients were cultured by two different methods.[5*] There was complete agreement in seven patients and disagreement in three. One patient had negative smears and cultures to the first technique. She had an old cervical laceration with thin purulent discharge, and marked tenderness and induration in the right adnexa, with a history of previous pelvic inflammation and exaggeration of symptoms for two months, which was the duration of the pregnancy. Eleven days later, she had a positive cervical culture and negative urethral culture by the second technique. She was not checked again by either method. It is most probable that she had a chronic infection and was harboring gonococci of low virulence, or she may have acquired a new infection in the interval. The second patient had positive urethral and cervical smears, and the cervix was negative to the first culture method. The following day, she had positive urethral and cervical cultures to the second method, and was not checked again by the first method. She complained of frequency and burning on urination for ten days, had urethritis, cervicitis, purulent vaginal discharge, and an ulcer on the vaginal wall with a positive Kahn test. The third patient had negative urethral and cervical smears on admission to the clinic, and repeated negative urethral and positive cervical cultures by the first method. One week later, urethral and cervical cultures were negative by both methods as were subse-

*See preceding footnote.

quent cultures during the antepartum period. She delivered four months later, had a normal puerperium and infant, and subsequent cultures were negative. The two culture methods agreed accurately in 70 per cent of the cases.

Smear Control Group

This group was collected from approximately 2,500 obstetric admissions over a period of one year, and is comprised of 44 patients admitted in labor, at term, who had not been cultured previously. Thirty-seven of these patients had positive urethral smears and negative cultures. Three had positive urethral smears and negative cultures, and negative cervical smears and cultures. Four patients had negative urethral smears and cultures, and positive cervical smears and negative cultures. The cervical specimens were taken at the time of aseptic vaginal examinations. The lochia from 15 of these patients was cultured, and all were negative. Eleven patients had late postpartum morbidity, with positive urethral smears and negative urethral and lochial cultures. Three infants born of these mothers had nonspecific ophthalmia. Three patients had condyloma acuminata of the vulva and two had Bartholin abscesses.

Stage and Site of Infection as Proved by Culture

Thirty-one patients had evidence of acute infection, and in nineteen patients the infection appeared to be chronic. Only the urethra was positive in twenty-two patients, and only the cervix in fourteen. Both the urethra and the cervix were positive in fourteen patients.

Associated Diseases

Five patients had primary syphilis, two late syphilis, one lymphopathia venereum, and of those patients examined for trichomonads, three were positive. Four patients had Bartholin abscesses, one Skenitis, one granuloma inguinale, five condyloma acuminata, two thrush vaginitis, and one patient had chronic salpingitis. One patient had acute arthritis throught to be caused by the gonococcus.

Treatment

Forty-four of the 50 patients with positive cultures were treated, and thirty-eight were negative after the first course. Six remained positive after the first course and received subsequent treatment. Three different therapeutic approaches were employed:

1. Sulfonamides orally, chiefly sulfathiazole, using approximately 40 grams in eight days. Eighteen patients were treated and sixteen were negative after the first course. One patient was negative after two courses, and one patient after three courses of treatment.

2. Local application was made to the vulva, vagina and cervix of an ointment containing 2 per cent allantoin, 15 per cent sulfanilamide, and 5 per cent lactose in a special greaseless base buffered to a pH of 4.5 with lactic acid.[6] This method was used only in patients who had positive cervical and negative urethral cultures, and was applied twice daily for ten days. Nine cases were treated, and eight were negative after the first course. One patient required a second course of treatment and remained negative thereafter.

3. A combination of the two afore-mentioned methods was employed in seventeen cases, and fourteen patients were cured after the first course, two after a second course, and one patient was still positive after two subsequent courses of local treatment. She then received another course of combined treatment and was negative. She was again positive in the clinic before delivery and probably was reinfected.

Sulfonamide blood levels were adequate in most cases, and adequate in those treatment failures in which levels were recorded. Patients on local treatment never had more than 1 mg. of sulfanilamide per 100 c.c. of blood.

There were four morbid patients and all occurred in the first few days post partum. There was no morbidity in the antepartum patients. Bed rest was insisted upon, even in the ambulatory antepartum patient, and was considered an important part of the therapy.

Condition of Mothers and Infants Following Delivery

Forty-three of the 50 culture-positive patients were delivered in hospitals, but only 27 were delivered in Gallinger Municipal Hospital. Twenty-six mothers delivered 26 premature and mature infants, and one patient delivered a previable infant. Eleven infants were males, and 15 were females. It was interesting to note the absence of genital disease in all infants. Two infants developed ophthalmia, both were gonococcal and subsequent cultures from the mothers were positive. The urethral smears from these mothers were negative on admission, but later urethral smears and cultures were positive post partum. One infant developed jaundice, two diarrhea, and one died of pneumonia. Twenty-four mothers were followed in the hospital after delivery for evidence of infection, and of this number, eight were diagnosed for the first time and treated, before follow-up. Two patients treated previously were positive to culture after delivery. Both had been treated adequately and confined continuously to the hospital subsequent to treatment and prior to delivery. Gonococci were recovered from the urethra in both patients. The first patient had positive urethral and cervical cultures after sulfathiazole. She was then treated with sulfanilamide, and had a negative culture from the urethra on day of delivery. The urethral culture was again positive on the seventh day post partum. The second patient had negative urethral and cervical cultures 14 days prior to delivery, and the urethral culture was positive 9 days after delivery. The show and lochia were negative in both cases, and both patients were considered cured following the succeeding course of treatment. The average time between diagnosis and delivery for 17 cases was 79 days. The greatest number of days between diagnosis and delivery was 225, and the fewest that of delivery.

Discussion

Since a positive diagnosis was based on isolation of *Neisseriae* from either the urethra, cervix, or both, 100 per cent of the 50 patients were positive to culture. Seventy-four per cent of patients had either positive urethral, or cervical smears, or both, and might have been diagnosed by smear alone. However, if smear alone had been used, 26 per cent of the cases positive to culture would have been missed. On the other hand, if only smear had been used for diagnosis in both the culture-positive

group (50 patients), and the smear positive-culture negative group (44 patients), 26 per cent of the culture-positive cases would have been missed, and 100 per cent of the smear positive-culture negative cases would have been falsely diagnosed positive. Thus, the state of confusion resulting from the use of smear and culture in the diagnosis of gonorrhea is explained. To corroborate the diagnosis by smear in the smear positive-culture negative group, eleven patients had late postpartum morbidity, three condyloma acuminata of the vulva, two Bartholin abscesses, all being suggestive clinical evidence of gonorrheal infection.

In the culture-control group, there was complete agreement in 70 per cent of the ten cases. In the three which disagreed, two cases can be eliminated because of a time interval between the two techniques, seven days in one case, and 11 days in the other. Both methods would have been positive in the third patient, if they had been repeated. Van Slyke, Thayer, and Mahoney report the findings of several laboratories using identical culture media, comparable inoculation techniques, and the use of identical secretions in 140 gonococci-positive culture cases. The closest any two laboratories could check on any medium was 75 per cent of the cases.[7]

While it is evident that culture is more efficient than smear in establishing a positive diagnosis, it has pitfalls. These are, in the main, dependent upon the virulence of the gonococcus, the manner in which specimens are obtained and stored prior to incubation, and the media and method of incubation employed. Nothing will be said of the difficulties encountered in cultural technique, but certain observations relating to the biology of the gonococcus can be utilized to increase the efficiency of culture. It was necessary to repeat cultures several times in several different patients before the gonococcus was isolated. This was done because the history and findings were suspicious. One patient had repeatedly positive smears, and the culture was not positive until repeated three times. The smear will occasionally reveal the presence of an intracellular diplococcus whose virulence is so reduced that it will not grow out on artificial media until activated, and can be recovered later, if a suspicious or positive smear has kept the examiner on the alert. The difficulty with smear is that it is also positive with a great variety of organisms other than *Neisseriae* which compose the flora of the female genital tract.[1, 4, 8, 9] The chief offenders are the species of the tribes *Streptococceae, Staphylococceae, Mimeae,* coccoid forms of the colon bacillus, and the gram-positive diplococcus which tends to lose the strain. It is important that an exhaustive examination be made of the vulva, urethra and adjacent ducts, the vagina, cervix and adnexa, and that specimens obtained at this examination, be used for smear and culture. The lower portion of the urethra should be expressed outwardly, and the contents of the cervical glands expressed by gently grasping the cervix between the blades of the speculum. Douching or voiding before collec-

tion of specimen,[10] will wash away or inhibit in some manner, the growth of the organisms. Thick lubricating jellies lead to errors in diagnosis,[11] probably by inhibiting growth, or mechanically interfering with proper plating of the specimen.

Very little difficulty was encountered in establishing a diagnosis in the acute infection, both the smear and culture being positive in the presence of acute inflammation. In the treated patient, or one harboring a chronic infection, the diagnosis was more difficult. The gonococcus may be deeply embedded in the glandular structures of the urethra and cervix, its virulence reduced, with only a mild chronic inflammatory reaction in the structures involved.

Three patients at term, in labor, were examined vaginally for obstetric complications, and the unsuspected cervix found infected. There was no history of infection, no suggestive symptoms, and no findings other than a cervicitis. Both the urethra and cervix should be examined in patients with a suspicious history or findings, even after the seventh month of pregnancy, but should be done with aseptic precautions. Aqueous Zephiran 1:1,000 was instilled into the vagina following examination, and was considered a valuable procedure.

Two patients were found to have infections from which *Neisseria catarrhalis* was isolated. One patient was five months pregnant when diagnosed. The urethral and cervixal smears showed typical gram-negative intracellular diplococci, and cultures from both sources subjected to fermentation studies revealed this organism. She had a mild urethritis and cervicitis, was treated with sulfathiazole by mouth, with clinical improvement and negative cultures. Five weeks later, she had a yeast vaginitis with negative cultures for *N. catarrhalis.* Four weeks later, cultures for yeast were negative but *N. catarrhalis* was again obtained from the urethra and cervix, which were mildly inflamed. She delivered at another hospital, and did not report back for follow-up. The second *N. catarrhalis* infection was found post partum, and was of no particular interest.

The gonococcus was not recovered from cultures of show and lochia. Since lochia possesses certain properties favorable to the artificial growth of this organism, i.e., serum with high hemoglobin content, alkaline reaction, and is incubated in the human body at optimum temperature in a moist anaerobic environment, it was anticipated recovering the organism in some cases. The proper pH for artificial growth of the gonococcus is (7.2 to 7.6,)[4] so an increased alkalinity of the lochia may be lethal as the gonococcus is destroyed rapidly in culture media with a pH above 8. Perhaps, the innumerable bacteria in the vagina of the gravid and puerperal woman may overgrow the more delicate gonococcus[2] on artificial media.

In ten postpartum patients, the gonococcus was recovered from the urethra. Eight were diagnosed for the first time, and two had been

previously diagnosed and treated. This is in accord with Dr. Curtiss who believes the urethra is often the site of persistent gonorrheal infection, and infections of the cervix less persistent than he formerly thought.[1]

Gonorrheal infection seemed more persistent and resistant to treatment in pregnancy. Six of the forty-four patients treated were still positive after the first course of treatment. Four of these six patients had negative cultures after two courses of treatment. One patient had negative cultures after three courses of treatment, and a single patient was still positive after a third course. It is impossible to be certain when a patient is free of infection following treatment, but in the light of present knowledge, patients should be followed closely for four to six months with frequent smears, cultures, and clinical evaluation. If there is no evidence of infection after this period, it is probable the patient no longer harbors the gonococcus.

Four patients were morbid in the first few days after delivery. Dr. DeLee states: "Acute infections are likely to show the exacerbation in the first few days of the puerperium, because of the associated streptococci and staphylococci while chronic gonorrhea causes the 'late fevers' in pus tubes or adhesive obliterating peritonitis, often, not always, leaving permanent sterility, and gynecologic invalidism."[2] As nearly as these four patients can be classified correctly at time of delivery, two had acute infections and two were cured, and will be discussed in that order. The first case was admitted at the ninth month of pregnancy, in active labor with a history suggesting infection. She had a Bartholin abscess, purulent urethral discharge, with a positive urethral smear and negative urethral culture. The urethral culture was repeated on the second postpartum day, when patient had an elevation to 102 degrees Fahrenheit and was positive. She was treated and subsequent cultures were negative. The second patient was admitted as an early abortion at the second month of pregnancy, and urethral smear was negative. She continued to bleed and sponge stick curettement of uterus was done. She was febrile on the second postpartum day, and urethral culture taken at this time was positive. She responded to sulfathiazole and subsequent cultures were negative. The third patient had a positive urethral culture at the sixth month of pregnancy, was treated and considered cured. She delivered at the tenth month, and was morbid from the third to the seventh postpartum days. Her cultures were negative for *Neisseriae* post partum. The fourth patient had a positive cervical culture when eight and one-half months pregnant. She was treated and subsequent cultures were negative. She delivered six weeks later, and was morbid on the third and fourth postpartum days. Urethral, vaginal, and later cervical cultures were negative for *Neisseriae*. There was no evidence of adnexal disease in any of these patients on discharge from the hospital. Both the acute and cured infections were morbid in

the first few days after delivery. In the two acute infections, gonococci were recovered from the urethra shortly after labor. In the two cured infections, considerable time had elapsed since treatment. The urethra was positive in the two acute infections, and had been positive in one cured infection. Only the cervix had been positive in the second cured infection. Apparently, the morbidity in the two cured infections was caused by organisms other than *Neisseriae*. In the control group by smear, eleven patients had late postpartum morbidity with positive urethral smears, and negative urethral and lochial cultures.

The author believes diagnosis by smear is more misleading in the pregnant patient though a comparative study was not made. The characteristic changes in the tissues of the pelvis in pregnancy, i.e., hypertrophy, softening, increased vascularity and glandular activity with increased hydrogen ion concentration of the vagina, inhibit the growth of certain organisms. But if the vagina or cervix become eroded, or there is abnormality of the secretion in the vagina, all sorts of organisms may be found which can cause confusion. A latent gonorrheal infection in the urethra or cervix may be stimulated by the changes of pregnancy, and a discharge recur from which gonococci can be isolated. In the pregnant patient, the vagina and vulva are frequently involved in the acute inflammatory process giving rise to more clinical evidence of disease.

Summary and Conclusions

Fifty obstetric patients have been examined by smear and culture in the antepartum, intrapartum, and postpartum periods and proved to harbor *Neisseriae* by cultural identification. Forty-four obstetric patients at term, in labor, with findings suggesting gonorrheal infection and/or positive smears but negative cultures, have been compared with the Neisseria positive group to demonstrate certain features relating to diagnosis, treatment, and management of Neisserian infection in pregnancy.

1. Culture is more efficient than smear in establishing a positive diagnosis in Neisserian infection in pregnancy.

2. Smear is valuable in conjunction with culture in establishing a positive diagnosis in chronic infections, and particularly in following treated patients for cure.

3. Repeated smear and culture at the time of a searching physical examination is the most adequate method of diagnosis. One negative smear and culture will not rule out gonorrhea.

4. *Neisseria catarrhalis* was isolated from 4 per cent of the patients. In the interest of an accurate diagnosis, and for the protection of patient and physician, fermentation studies should be done to identify the particular Neisseria present.

5. The gonococcus was apparently activated by the trauma of labor, and recovered from the urethra post partum, in two treated patients who had negative cultures before labor.

6. The gonococcus was recovered from the urethra of eight postpartum patients not previously diagnosed or treated.

7. The gonococcus was not recovered from the show or lochia of patients proved to harbor the infection in the urethra or cervix.

8. Two patients with acute gonorrhea, and two with cured infections had early postpartum morbidity with clinical endometritis.

9. Gonorrheal infection appeared more persistent and resistant to treatment in pregnancy.

10. Diagnosis by smear seemed more confusing in the pregnant than in the nonpregnant female.

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CORTICAL NECROSIS OF KIDNEYS ASSOCIATED WITH NECROSIS OF PITUITARY IN OBSTETRICAL SHOCK

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POSTPARTUM necrosis of the anterior lobe of the pituitary gland has been described numerous times and is becoming a well-known clinical entity. Likewise, the occurrence of bilateral renal cortical necrosis in pregnancy, in shock, in infections, and of undetermined origin has been described. No cases are found in the literature available describing a combination of necrosis of the anterior lobe of the pituitary gland and bilateral renal cortical necrosis following parturition. It is the object of this paper to report such a case.

Case Report

The patient, a white female, aged 28, married, was first admitted to the hospital on July 14, 1942, when she had a spontaneous delivery of an anencephalic monster of 8 months' gestation. There were no complications during the pregnancy or delivery. At this time she had one child, aged 22 months.

She was next seen at the outpatient obstetrical clinic June 16, 1943; her last menstrual period was April 17, 1943, and the estimated date of confinement was January 24, 1944. Physical examination at this time was normal. She attended the clinic regularly and September 20, 1943, was admitted to the hospital for back pain and nocturia of one day's duration. Physical examination was negative. Hemogram revealed hemoglobin 70 per cent (Tallqvist), 3,850,000 erythrocytes, 7,250 leucocytes; differential, 74 neutrophiles, 1 eosinophile, and 25 lymphocytes. Blood serology was negative. Urine analyses for this admission are given in Table I.

TABLE I. URINE ANALYSIS, SEPTEMBER, 1943, ADMISSION

			MICROSCOPIC			
DATE	ALBUMIN	SUGAR	CASTS	PUS CELLS	BLOOD CELLS	CATHETERIZED
9/20	+	0	0	++++	0	No
9/21	0	0	0	++++	0	Yes
9/22	0	0	0	++++	0	No
9/23	0	-	0	++	+	Yes
9/25	++	0	0	-	++++	No
9/26	0	0	0	0	++++	No
9/27	0	0	0	0	0	No
9/28	0	0	0	0	0	No

She received sulfadiazine until hematuria appeared on September 24, 1943, when it was stopped and mandelic acid therapy was started. She was discharged on September 28, 1943, with a diagnosis of pyelocystitis (right) of pregnancy. Following discharge, she was followed in the clinic with no recurrences or further difficulties until she returned to the

hospital on December 25, 1943, with fever, pain and tenderness in the right costovertebral angle of two days' duration. Temperature on admission was 102° F., rapidly falling to normal in two days. Hemogram was hemoglobin 65 per cent (Tallqvist), 3,450,000 erythrocytes, 5,250 leucocytes; differential was 68 neutrophiles, 2 eosinophiles, and 30 lymphocytes. The urine on admission showed three-plus pus cells with a few erythrocytes, no albumin, and it continued to show pus cells, but no more erythrocytes. She was placed upon sulfadiazine on admission with good response. Due to the holidays, the patient insisted upon discharge and went home December 31, 1943.

Her last admission was on January 6, 1944, with complaint of cough, backache, fever, and sordes of mouth. Her condition had been fair during the interval, and the day of admission was the first time she had a fever (100° F.).

Physical examination revealed multiple sorders of the tongue and mouth. Heart and lungs were negative. Blood pressure was 120 mm. of mercury systolic, and 80 mm. of mercury diastolic. The uterus was two fingerbreadths below the xiphoid, deflected to the left, with the buttocks in the fundus and soft parts to the right. The head was floating above the symphysis. Fetal heart rate was 140 per minute. Chest roentgenogram was negative. Sedimentation rate was 90 mm. per hour (Westergren). Blood serology was negative. The clinical laboratory data are tabulated in Table II.

Course in Hospital.—The patient ran a fairly even course on January 7, 8, and 9, with her temperature gradually climbing to 103° F., when she was placed on a sulfadiazine routine.

January 10.—Temperature 104° F. Few uterine contractions, head not engaged, fetal heart fast. Transfusion (citrate method) of 500 c.c. of blood at 2 P.M., with no reactions.

January 11.—Temperature 103.5° F. Condition unchanged.

January 12.—Temperature 103° F. Fetal heart tones have disappeared, and cervix was dilating slowly. Sulfadiazine discontinued.

January 13.—Taken to operating room at 9:50 A.M. and under ether and ethylene anesthesia midforceps extraction of a female stillborn child was performed at 10:12 A.M. with an episiotomy. The placenta was not expelled, and was manually removed in fragments at 11:20 A.M. It was estimated that the blood loss did not exceed 300 cubic centimeters. The patient went into severe shock, almost dying on the table, and was given blood, plasma, fluids, and cardiorespiratory stimulants. Blood pressure was not recorded in operating room; on return to ward it was 90 mm. of mercury systolic and 60 mm. of mercury diastolic. At 10:00 P.M. blood pressure was 95 mm. of mercury systolic and 60 mm. of mercury diastolic and the patient was comatose.

January 14.—The patient vomited at intervals. Temperature fell from 101° F. at 1:00 A.M. to 97° F. at midight and 96° F. at 4:00 A.M. the following morning.

January 15.—Vomiting, drowsy, condition critical. Anuric. Ureters lavaged, but no crystals were obtained, and no obstruction was encountered.

January 16.—Patient almost totally anuric. Blood pressure 120 mm. of mercury systolic and 72 mm. of mercury diastolic. Involuntary liquid stools today.

TABLE II. CLINICAL LABORATORY DATA, LAST ADMISSION

DATE 1944	URINE									HEMOGRAM							BLOOD CHEMISTRY				
						MICROSCOPIC															
	COLOR	APPEARANCE	REACTION	SPECIFIC GRAVITY	ALBUMIN	CASTS	PUS CELLS	BLOOD	CATHETERIZED	HEMOGLOBIN (% SAHLI)	ERYTHROCYTES (MILLIONS PER C.MM.)	LEUCOCYTES (THOUSAND C.MM. PER C.C.)	NEUTROPHILES	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	NONPROTEIN NITROGEN (MG. PER 100 C.C.)	CREATININE (MG. PER 100 C.C.)	GLUCOSE (MG. PER 100 C.C.)	SULFADIAZINE (MG. PER 100 C.C.)	ICTERUS INDEX
1/ 6	amb.	cloudy	acid	1.012	++	0	loaded	+	no	56	2.85	7.6	53	3	1	41					
1/ 7	–	–	–	–	+	0	++++	+	yes												
1/ 8																					
1/ 9																	20.4		80.0		
1/10	yel.	cloudy	acid	1.017	0	0	+	+++	no	50	3.06	5.2	62	3	–	35	20.1				
1/11	amb.	cloudy	acid	1.015	–	0	loaded	0	no	50	3.15	4.6	60	3	1	36				13.5	
1/12	amb.	cloudy	acid	1.015	+	0	loaded	0	no	56	3.24	5.0	63	2	–	35	22.9			15.0	
	Delivery 1/13/44 at 11:20 A.M.																				
1/13	red	cloudy	acid	1.014	+	0	++	++	no												
1/14	amb.	cloudy	acid	1.010	+	few gran.	+	+++	no	42	2.36	5.2					55.1	3.4	50.0		
1/15	anuric									36	1.70	4.0	62	2	–	36	80.4	5.9	90.0		
1/16	red	smoky	acid	1.008	++	0	0	all blood	no	36	1.65	3.7	61	2	–	37	90.2	6.0			
1/17	red	smoky	alk.	1.009	++	0	0	all blood	no	26	1.46	9.0	73	2	1	24	105.8	9.9			5
1/18	red	smoky	acid	1.012	++	0	0	all blood	no	20	1.27	19.0	62	2	1	35	137.6	9.9			

January 17.—Voided 80 to 100 c.c. of urine. Some dyspnea and cyanosis present. Given oxygen.

January 18.—Still partially anuric (voided 250 c.c. in twelve hours). Condition very grave.

January 19.—At 2:00 P.M. a transfusion of 500 c.c. of blood (citrate method) was given, with no reaction. The patient expired at 6:13 P.M.

Autopsy Findings.—The body weight was 128 pounds and length, 66 inches. The breasts were engorged and milky fluid was easily expressed. There was massive perineal ecchymosis and a posterior episiotomy suture line.

The brain showed no gross softening, congestion, or hemorrhage. The ventricles were not dilated. Cerebrospinal fluid was clear and of normal amount. The pituitary gland was swollen, tense, and impinging on the infundibulum. It measured 2.3 by 1.5 centimeters. Following fixation in formol-alcohol, sectioning revealed a narrow 2 to 3 mm. rim of darker viable tissue around the anterior lobe surrounding the central soft, yellow-white, necrotic area (Figs. 1 and 2). The sella turcica showed no enlargement.

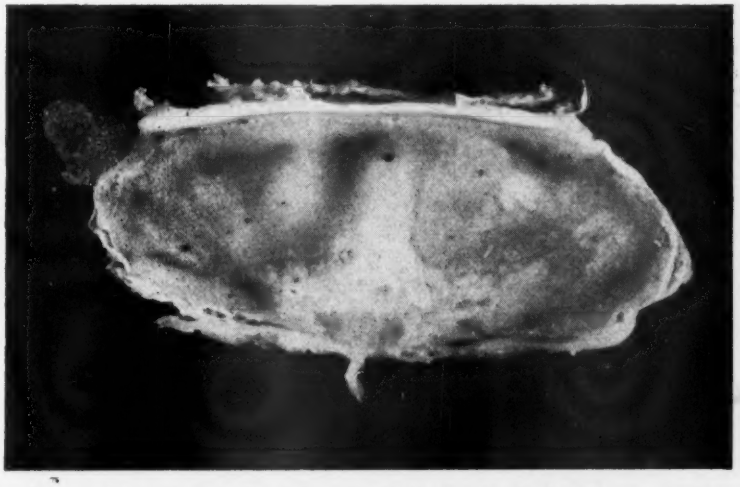

Fig. 1.—Cut surface of anterior lobe of pituitary gland showing central necrosis. (Formol-alcohol fixation.) (Magnification ×6.)

There were no gross changes in the throat or neck. The thyroid was symmetrical and weighed 35 grams. The pleural spaces were clear. The lungs showed congestion with terminal bronchopneumonia involving the upper and middle lobes of the right lung. There were no infarcts and the pulmonary artery contained no emboli.

There was no increase in pericardial fluid. The heart weighed 300 grams and showed no gross changes or anomalies. The aorta was smooth, elastic, and showed no stenosis or dilatation.

There were no adhesions or increased fluid in the abdominal cavity. The liver protruded 4 cm. below the costal border. The diaphragm was not elevated. The liver was tense, pale red brown, and the cut edges bulged. There was no gross hemorrhage or infection.

The spleen was congested, swollen, and soft; it weighed 320 grams. The capsule was smooth, blue purple; the cut surface was dark, soft, and semifluid. There was no gross hemorrhage, infarction, or infection.

The pancreas and adrenals showed no gross changes.

The kidneys weighed 340 grams combined. There was moderate dilatation of the right ureter and pelvis with minimal dilatation on the left. There was no ureteral obstruction demonstrable in situ. The mucosal ureteral surfaces were edematous, yellow, and mucoid, but no hemorrhage, debris or crystals were present. They each contained 6 c.c. of yellow, thick urine; culture of this revealed organisms of the genus *Aerobacter*. The kidneys showed multiple confluent areas of yellow-white cortex surrounded by zones of hyperemia. The capsules stripped easily, seeming to be lifted by subcapsular fluid. The cut surfaces showed zones of yellow-white cortex surrounded by hyperemic tissue (Fig. 2). The necrotic areas had lost all the usual cortical markings except where there was a narrow 1 to 2 mm. zone of viable tissue supplied by capsular vessels. In areas, the columns of Bertini were dark red brown, and seemed to be the sites of some hemorrhage and central necrosis. There were no grossly recognizable thrombosed vessels present. There was slight blunting of the papillae in the right kidney with very minor dilatation of the calices. The mucosal surfaces were moderately granular and hyperemic. No crystalline or amorphous deposits were present.

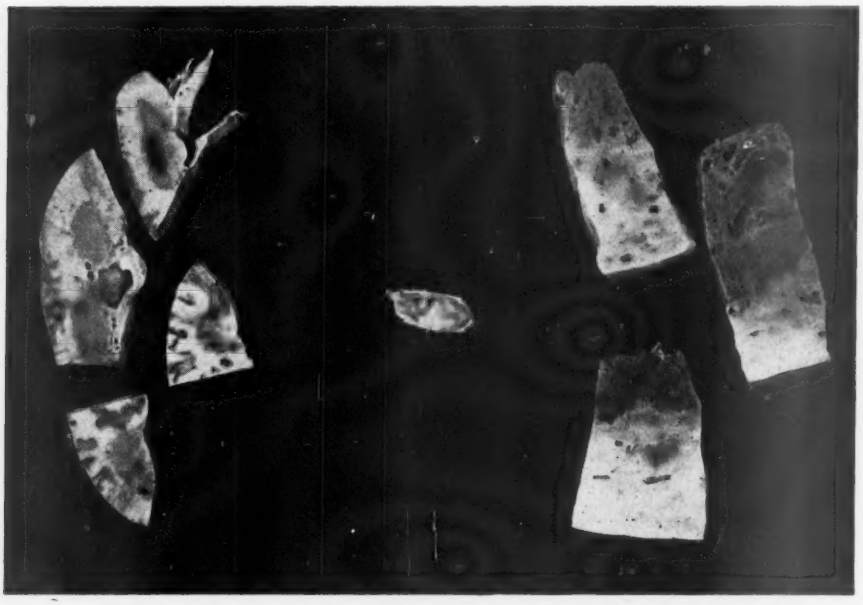

Fig. 2.—Cut surfaces of kidneys (left), anterior lobe of pituitary gland (center) and uterine wall (right). (Formol- alcohol fixation.) (Slightly reduced.)

The urinary bladder contained 10 c.c. of lemon-yellow, cloudy urine. The mucosa around the trigone was injected. There were multiple retroperitoneal organized hemorrhages present around the bladder.

The uterus measured 25 cm. from fundus to cervical constriction, 20 cm. between the Fallopian tubes, and 12 cm. in depth at the midportion. The serosa was thickened, white, and free from exudate or hemorrhage. The Fallopian tubes and ovaries were normal, postpartum in character. There was marked hemorrhage beneath the peritoneal covering at the

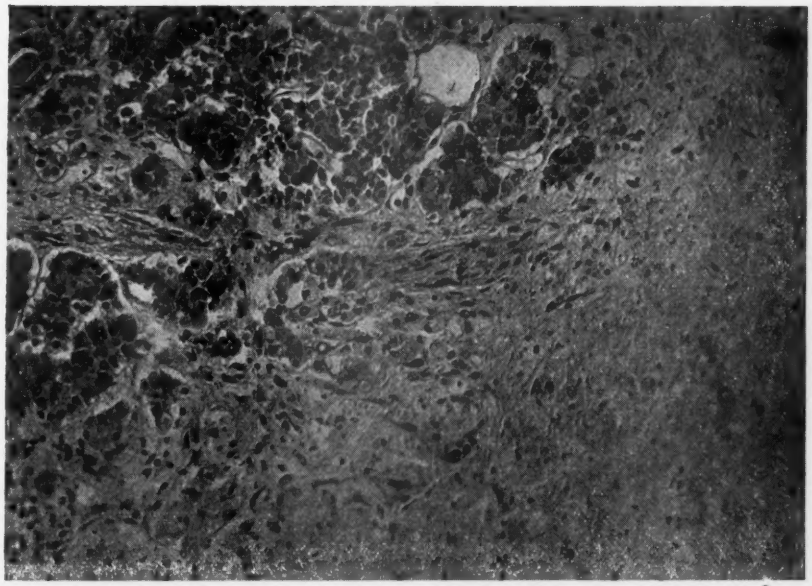

Fig. 3.—Section through edge of anterior lobe of pituitary gland showing viable cells and junction of necrosis. (Magnification ×800.)

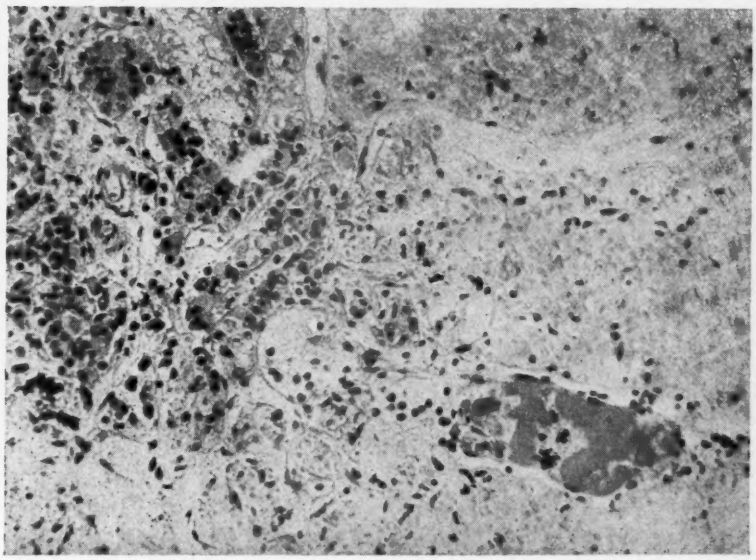

Fig. 4.—Section through necrotic area in anterior lobe of pituitary gland showing thrombosis of vessels. (Magnification ×800.)

level of the internal orifice. This became confluent with hemorrhages in the vaginal walls and extended laterally and posteriorly to encompass the entire pelvis up to the sacral promontory. The uterine walls measured 1.5 to 2.0 cm. in thickness, and attached to the inner surface was a 2 to 3 cm. edematous, hemorrhagic mass of fibrin and fibrous-like tissue (Fig. 2). The sinuses in the uterine wall were dilated and filled with thick, unclotted blood. The external orifice was a ragged rim of hemorrhagic, torn tissue. The vaginal walls showed four incomplete vertical tears extending into, but not through the muscular layer. There was considerable hemorrhage into the rectovaginal septum with extension into the ischiorectal fossae.

There were no gross changes in the gastrointestinal tract.

Microscopic examination of sections from the brain, thyroid, heart, adrenals, pancreas, intestine, diaphragm, and skeletal muscle showed no noteworthy histologic changes. The liver sections showed minor congestion with no inflammation or degeneration. The lung showed an early bronchopneumonia.

Sections from the anterior lobe of the pituitary gland showed a rim of congested viable pituitary cells in which typical acidophilic "pregnancy cells" were present (Fig. 3). The viable cells surrounded a large area of acellular debris representing ischemic necrosis of the major portion of the gland. In these areas, shadowy outlines of cells could be seen surrounding small thrombosed arteries and veins (Fig. 4). Away from these areas, the endothelial spaces were mostly collapsed, but in a few thrombosis was easily recognized. There was no evidence of infection or tumor.

Sections of the kidneys showed an abrupt transition from viable to necrotic areas in the cortex. The necrosis was complete and only shadows of cells could be seen. The general architecture remained and the vessels were engorged with some necrosis of their walls and occasional rupture (Fig. 5), especially of the intralobular arteries which almost always contained thrombi. The glomeruli were pale, necrotic in such areas, and it was possible to trace a thrombus from an afferent arteriole (Fig. 6), back to its (the afferent arteriole) intralobular origin. There was a marked absence of inflammatory reaction or exudate in the necrotic areas, but hyperemia, exudate, and edema surrounded such areas. The tubules showed granular and cellular debris with some casts. In areas of the kidney that were not grossly necrotic, there was a very minor inflammatory reaction along the tips of the papillae and the mucosal surfaces. There was no evidence of glomerulonephritis or of interstitial nephritis.

Sections from the uterus showed the usual muscle hypertrophy with edema and congestion. No endometrial structures could be seen. The approximate region of the endometrial base faded into edematous eosin-staining fibrillar structures with no nuclear or cytoplasmic outlines. No histologic evidence of placenta accreta could be seen. There was a remarkable lack of inflammatory or phagocytic activity in these sections.

Gross and microscopic examination of the stillborn baby in this case showed no evidence of changes beyond some intrauterine maceration and forceps marks on the head.

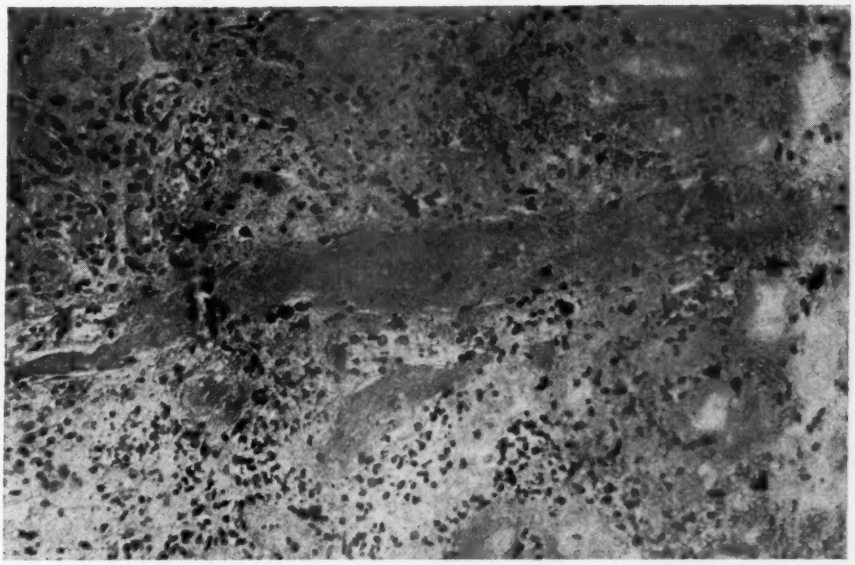

Fig. 5.—Section of kidney showing thrombosis and rupture of an intralobular artery. (Magnification ×800.)

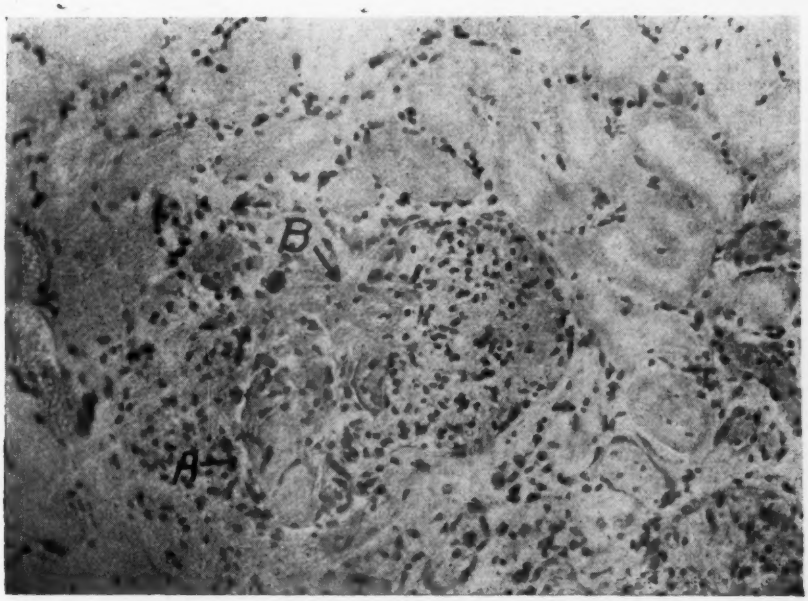

Fig. 6.—Section of kidney showing thrombosis of afferent arteriole at *A*, entering thrombosed glomerulus at *B*. (Magnification ×800.)

Discussion

Numerous case reports[1-4] have been published of postpartum necrosis of the anterior lobe of the pituitary gland following Sheehan's[5] first paper reporting 11 cases studied at autopsy, and he has summarized the reported autopsy cases in another later paper.[6] From his studies, he believes that the necrosis starts about the time of delivery, is due to thrombosis and not embolism of the pituitary sinuses, and is usually consequent upon the collapse of the patient following severe hemorrhage often as a result of a retained placenta. Such factors were certainly present in the case reported here.

Hutchinson[7] reported a case of necrosis of the anterior lobe of the pituitary gland during pregnancy in which the patient was approximately two months pregnant. At autopsy a pulmonary embolus probably from septic endometritis was found along with necrosis of the anterior pituitary gland. In this case there was no hemorrhage, but the patient was in extreme shock following the pulmonary embolus, and expired approximately forty hours later. The histologic picture of the necrotic pituitary gland was estimated to be of thirty-six to forty hours' duration following the criteria set forth by Sheehan.[5]

Ash[8] has summarized the literature on bilateral cortical necrosis of the kidneys up to 1933. Of the 44 authentic cases he collected, 34 complicated pregnancy, and of the 18 cases about which there might have been some question, 8 were in pregnancy, giving a total of 62 possible cases, with 42 of these occurring in pregnancy. He states from this material: "The evidence indicates that the thrombosis is secondary, not to the necrosis, as some would claim, but to the stasis. The thrombi begin in the afferent arteries and extend in a proximal direction to the limit of the necrosis, so that they rarely go beyond the interlobar arteries. They are rare in the glomeruli, efferent arteries and veins. The blood in these vessels is 'stale' and so may have lost some of its coagulability. The exudate does not represent a primary inflammatory reaction as much as it does the reaction to necrotic tissue."

De Navasquez[9] feels that the kidneys prior to the onset of symmetrical cortical necrosis of pregnancy are histologically normal and the primary change is necrosis of the peripheral intralobular arteries producing ischemia, and necrosis with the thrombosis being a terminal picture resulting from the stasis thus produced. He reports 12 additional cases associated with pregnancy.

Dunn and Montgomery[10] feel that extreme glomerular capillary dilatation with loss of plasma producing inspissation of the blood and blocking of the circulation at this level is the ultimate factor in bilateral cortical necrosis. He feels it is possible to classify the condition as follows: "(I) Inflammatory, in acute necrotizing glomerulonephritis; (II) ischaemic, in the cortical necrosis of the renal toxaemias of pregnancy; and (III) venostatic, in acute thrombosis of the renal vein."

Godwin and McCall[11] reported a case of bilateral cortical necrosis of the kidneys in a man who died with peritonitis following perforation of a gastric ulcer. They felt that bacterial toxins were probably responsible for the cortical necrosis, but that shock with its resulting capillary stasis might have been a contributing factor.

McFarlane[12] describes a typical case of bilateral renal cortical necrosis that followed multiple fractures with internal hemorrhage, and he was

sure that any bacterial or toxic factor could be excluded, and that shock was the direct cause.

Penner and Bernheim[13] in a series of experiments with dogs produced severe shock by the intraperitoneal and intrapleural injection of epinephrine hydrochloride. In some of their animals, they found cases of bilateral cortical necrosis of the kidneys which were similar to those that had been reported in human beings and to the human cases they had studied. They felt that the vasospasm which occurs in shock was of sufficient intensity and duration to result in the kidney lesions in some instances.

In the case reported here, there were no signs of eclampsia and no autopsy evidence of the usual toxemias of pregnancy. The patient had a severe operative delivery with considerable frank bleeding, and more concealed bleeding internally. Severe shock developed and following this anuria, drowsiness, fall of temperature, and a persistent hypotension occurred. There was a steady rise in the nonprotein nitrogen and creatinine, with onset of vomiting and diarrhea. The gradual loss of hemoglobin and erythrocytes must have occurred as a result of bleeding from the kidneys, inasmuch as the icterus index was not elevated and there were no other bleeding points.

Summary

In the case reported here, there was combined necrosis of the anterior lobe of the pituitary gland and the cortices of the kidneys. The histologic picture of the pituitary and kidney changes was compatible with five to six days' thrombosis. The clinical picture was typical, and no evidence of other factors was found at autopsy. The collapse and shock at delivery was extreme, and it is felt that the changes found were initiated then. Added support is given to the belief that postpartum necrosis of the anterior lobe of the pituitary gland and bilateral renal cortical necrosis may be caused, in many instances, by severe shock in reporting here a case showing both of these conditions occurring simultaneously in the same patient.

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MASSIVE OBSTETRIC HEMORRHAGE REQUIRING HYSTERECTOMY*

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ACCUMULATING evidence[2-4] indicates that obstetric hemorrhage is now the most important and perhaps the most frequent cause of maternal mortality. Faulty or delayed obstetric hemostasis and the failure properly to replace the volume of blood which has been lost through hemorrhage are responsible for the mortality in most of these cases.

Simple and well-known conservative obstetric procedures can control the vast majority of obstetric hemorrhages if diagnosis is prompt and procrastination does not delay therapy. In a small group of cases, about one in a thousand in experience at the Mayo Clinic, however, these simple measures are ineffective owing to a pathologic process in the fundus or the lower segment of the uterus. The uterus may be ruptured, or on occasion, a true Couvelaire uterine bleeding accompanying abruptio placentae cannot be controlled by proper tamponade. Furthermore, instances of placenta previa or of leiomyomas of the uterus are encountered in which hemorrhage may be uncontrollable by vaginal procedures. Palpation on vaginal examination of the uterus and lower uterine segment usually will establish the diagnosis of uterine rupture. Abdominal exploration usually with hysterectomy is the only method which offers hope of effectively stopping these severe hemorrhages. Although the number of patients who have severe hemorrhage which cannot be controlled by simple obstetric procedures is small, they will contribute inordinately to the maternal mortality rate unless properly handled. Such patients probably would die of hemorrhage if abdominal exploration and surgical treatment are not performed, even though large volumes of blood are replaced.

Since the obstetric service was organized as a Section in the Mayo Clinic in 1922, there have been approximately 10,178 deliveries with five maternal deaths from hemorrhage, an incidence of 0.491 per 1,000 births. The first hysterectomy for obstetric hemorrhage in this series of patients was done July 3, 1935. From July 3, 1935, to May 31, 1944, inclusive, there have been 5,620 deliveries and eight patients have been treated by hysterectomy for hemorrhage. There was one maternal death from sepsis in these patients which was primarily caused by hemorrhage with a mortality of 0.178 per 1,000 births or 0.0178 per cent. This death was not one of the eight patients subjected to hysterectomy.

Report of Cases

CASE 1.—A primigravida, 31 years of age, had made twelve prenatal visits during which it was noted she had a fibroid uterus. Spontaneous

*Read at Minnesota Society of Obstetrics and Gynecology in Duluth, July 1, 1944.

delivery of a normal female infant weighing 3,842 Gm. occurred after an uneventful labor. Because of repeated intractable postpartum hemorrhages which could not be controlled by the usual measures employed for postpartum hemorrhage including proper uterine tamponade, subtotal hysterectomy was performed. The specimen removed included a degenerating cervical fibromyoma measuring 6 cm. in diameter.

CASE 2.—This patient had been receiving regular prenatal care at the clinic and was in the thirty-eighth week of her pregnancy when she complained of sudden rather severe pain in the right lower part of the abdomen and flank. Her only previous pregnancy had been terminated at the clinic by an elective, classical cesarean section because of a contracted pelvis.

Physical examination revealed tenderness, grade 3 on a grading basis of 1 to 4, over the right costovertebral region. Examination of a catheterized specimen of urine revealed pus, grade 4. The right ureter was then catheterized and a considerable quantity of cloudy urine was drained under pressure. This procedure relieved the patient's symptoms, so that she slept most of the night. She was observed in profound shock early the following morning. A diagnosis of intra-abdominal hemorrhage, probably from a ruptured scar of a cesarean section, was made. The shock was treated with intravenous administration of blood substitutes and whole blood so that hysterectomy could be carried out. Recovery was uneventful. It was interesting in this case to notice how completely the early signs of uterine rupture were obscured by the symptoms and findings of infection of the urinary tract.

CASE 3.—This patient, a primigravida aged 47 years, had been married three years without conception. She had made thirteen prenatal visits to the clinic since the fourth month of gestation. The pelvis was nearly normal being only slightly contracted throughout. The patient was allowed to go two weeks beyond the expected date of delivery because, although the fetus was large, it presented by the vertex and the pelvic capacity seemed to warrant a test of labor, until the last prenatal visit when the head was floating and overriding.

The patient was admitted to the hospital and an elective cesarean section was to be carried out the following morning. During the night after admission, she suddenly awoke because of vaginal bleeding and abdominal pain. The uterus was tense but the fetal heart tones were regular at 140 beats per minute. A diagnosis of abruptio placenta was made and a classical cesarean section was done at once delivering a normale male infant weighing 3,640 Gm. (8 pounds and 10 ounces) that survived.

There was some difficulty in detaching an infarcted, fibrotic portion of the placenta which measured about 2 by 2 cm. near the inferior angle of the uterine wound but no bleeding came from this part of the uterus after the placenta was removed. The uterus appeared normal on gross inspection and contracted well, so it was packed and closed in the usual manner. However, at the completion of the operation while the patient was still on the operating table, a tremendous uterine hemorrhage occurred through the pack. The vagina was tightly packed and hysterectomy was carried out at once. During much of the time consumed for these two procedures the patient was in various degrees of shock. Fluids were given intravenously in both arms simultaneously as follows: blood 3,400 c.c.; solution of dextrose 2,500 c.c.; and solution of acacia 1,000 c.c., a total of 6,900 c.c. of fluid. The concentration of hemoglobin was

15.2 Gm. per 100 c.c. before delivery, and it was 5.8 Gm. after the fluids were given. It may be calculated, therefore, that this patient lost practically her entire supply of blood by hemorrhage. Incidentally, 2,900 c.c. of blood came from group O donors while the patient was group B and yet, no agglutination phenomena occurred.

CASE 4.—A woman, aged thirty-two years, who was in her fourth pregnancy, was referred to the clinic in the third month of this pregnancy because of an anemia. The concentration of hemoglobin in the blood was 8.4 Gm. per 100 cubic centimeters. Large doses of iron were administered, but the concentration of hemoglobin was unchanged. Gastric analysis was advised but the patient did not obtain this test. At this time, some vaginal bleeding began and hospitalization was advised and refused. The patient went elsewhere, and it was learned subsequently that cesarean section had been performed because of a diagnosis of placenta previa. Tubal sterilization was said to have been effected at the time of the cesarean section.

This woman was next seen about a year and a half later when she was admitted to the obstetric service in the hospital in shock. A diagnosis of ruptured uterus from separation of the scar of a cesarean section was made and confirmed during the course of a supravaginal hysterectomy. From the history the rupture had taken place near the date of her expected delivery. It had occurred nearly twelve hours before admission, but her physician in her home locality had been called only in time to bring her directly to the hospital. The patient's convalescence was somewhat stormy, and was complicated by a rather severe psychosis developing on the twenty-fourth postoperative day. It was felt that the psychosis could have been due to cerebral damage on a circulatory basis from prolonged and profound shock.

CASE 5.—A patient, aged thirty-seven years, was admitted near term of her fourth pregnancy bleeding from what proved to be a marginal placenta previa. Rupture of the membranes alone controlled the bleeding. She was delivered of a normal infant weighing 3,800 Gm. by outlet forceps. The child survived. Because of an uncontrollable postpartum hemorrhage through a properly applied intrauterine pack, total abdominal hysterectomy was done.

CASE 6.—The patient, a primigravida aged 35 years, was referred to the clinic because of uterine pain and vaginal bleeding. From the history it was found that her systolic blood pressure had been as high as 150 mm. of mercury two years before admission, and that her systolic blood pressure had been as high as 200 mm. of mercury and had not been lower than 180 mm. in the past two months. It had been associated with albuminuria, grade 4 on a grading basis of 1 to 4. Four days prior to admission, she had had a slight episode of vaginal bleeding with irregular uterine contractions for twenty-four hours, following which she did not feel life.

On admission to the hospital the patient complained of severe, constant abdominal pain. Her blood pressure was 130 mm. systolic and 90 diastolic, the pulse rate was 100 per minute and she appeared pale and weak. Vaginal bleeding was active. A diagnosis of abruptio placentae was made. The cervix barely admitted the examining finger. The patient was given 2 liters of blood and a Porro-cesarean section was performed. The uterus was extensively infiltrated by blood and was so friable that the finger could be inserted through the uterine wall without much pressure.

CASE 7.—The patient was 28 years old and in her second pregnancy. Her first pregnancy had been terminated by cesarean section eleven years previously because abruptio placentae was suspected. She was admitted at term with classic symptoms and findings of a ruptured uterus from a scar of a cesarean section. This diagnosis was confirmed when an immediate hysterectomy was performed.

CASE 8.—The patient, gravida ix, para viii, had rapid, uneventful first and second stages of labor with spontaneous delivery of a normal living infant, weighing 3,920 grams. Because of an immediate and profuse postpartum hemorrhage, the placenta was removed manually after one attempt at expression. The uterus became atonic; because hemorrhage continued, the lower segment of the uterus, cervix and vagina were firmly packed and 1,000 c.c. of blood were given. The patient's condition was good after the transfusion. About twelve hours after delivery, the packing was removed and the patient promptly went into mild shock. She did not respond to the administration of intravenous fluids and blood to a satisfactory degree and reverted into shock soon after this treatment. External vaginal bleeding was negligible. Because of the presence of shock and the fact that progressive abdominal distention and pain developed, a diagnosis of ruptured uterus was made and confirmed at the time of hysterectomy. The rent was in the lower segment of the uterus, cervix and vagina on the right side. The vaginal laceration extended nearly to the introitus. This uterine rupture must have been caused either by a somewhat too vigorous attempt to pack firmly the entire genital tract or by the violent, rapid labor which the patient had. Administration of 3,500 c.c. of blood was required to carry the patient through the period of hemorrhage and the hysterectomy. In spite of this treatment, she went into deep shock on two or three occasions, although the concentration of hemoglobin in the blood one day after operation was 10.3 grams. Interestingly enough during the period of hemorrhage, the concentration of hemoglobin was 13.6 Gm. owing to the hemoconcentration.

Comment

The age of these patients varied from 27 to 47 years with an average age of 34 years. The parity ranged from none to eight and averaged two (Table I).

TABLE I. SURVIVING CHILDREN OF THE EIGHT MOTHERS WHO UNDERWENT HYSTERECTOMY FOR OBSTETRIC HEMORRHAGE

CASE	CHILDREN LIVING	
	BEFORE LAST PREGNANCY	AFTER DELIVERY AND HYSTERECTOMY
1	0	1
2	1	1
3	0	1
4	4	4
5	3	4
6	0	0
7	1	1
8	8	9
Total	17	21
Average	2.1	2.6

The cause of the extensive hemorrhage in the eight cases was as follows: ruptured uterus in four cases; severe abruptio placenta in two

cases and intractable postpartum hemorrhage associated with placenta previa and uterine fibromyoma one case each.

Six of the eight patients received prenatal care at the clinic, and when I reviewed the records, I considered the prenatal care adequate except for one error in judgment. The patient's cooperation in this case too was open to question. In the two other instances, the prenatal care was not adequate. One of these patients did not seek medical attention throughout her pregnancy until after the uterus had ruptured near the date of her expected delivery. In the other case, gross findings of a severe hypertensive toxemia were manifest for two months before adequate treatment was instituted. In general, the severe hemorrhages suffered by these patients could not have been prevented by prenatal care alone. These hemorrhages must properly be termed sudden, serious "accidents of pregnancy." However, more vigilant and effective prenatal care might have averted three of the four fetal disasters, and avoided such severe hemorrhages as to deprive three of the patients of their uteri.

Maternal puerperal morbidity was 100 per cent as judged by the standard advised by the American Committee on Maternal Welfare. Four patients, however, did not have a rise of temperature to more than 101.2° F. The more severe febrile reactions were observed among patients who had ruptured uteri wherein large volumes of blood had been present in the peritoneal cavity. Sulfonamide therapy has been used intraperitoneally in the recent cases. Chemotherapy also has been employed orally or parenterally later in the postoperative period when indicated. There were no maternal deaths in this series.

There were four fetal deaths, or a mortality of 50 per cent. All of these deaths were prior to delivery, and in three of them, the fetus was known to have expired before admission of the mother to the hospital. Rupture of the uterus was the cause of three fetal deaths, and abruptio placenta accounted for the fourth. The fetal survival in this group of cases is improved when the babies which have been born previously by these mothers are considered. The eight women had had a total of seventeen normal surviving infants before the pregnancy under consideration, an average of 2.1 each. Including the four infants that survived the pregnancies under discussion, there was a total of twenty-one living babies, or an average of 2.6 for each mother. Only one of the eight mothers was left without a surviving infant after hysterectomy.

Shock was present in each of these cases of severe hemorrhage and in five, it was profound. In four cases blood pressure could not be elicited for a time, and in several instances positive pressure was needed to obtain a flow of intravenous fluid.

The volume of hemorrhage sustained by these women was large and often tremendous. Large volumes of blood or blood substitutes, or both, were required to keep them out of dangerous shock and to carry them

TABLE II. TYPE AND VOLUME OF FLUID REPLACEMENT GIVEN INTRAVENOUSLY

CASE	FLUIDS GIVEN INTRAVENOUSLY				BLOOD, PER CENT	HEMOGLOBIN, GM. PER 100 C.C.	
	BLOOD C.C.	BLOOD SUBSTITUTE C.C.	GLUCOSE OR SALINE SOLUTION C.C.	TOTAL C.C.		2 TO 5 DAYS POST-OPERATIVE	AVERAGE
1	500	1,000	500	2,000	25	8.0	
2	1,000	1,000	2,800	4,800	21	7.6	7.1
3	3,400	1,000	2,500	6,900	49	5.8	46.0%
4	2,500	0	450	2,950	85	6.8	
5	3,000	0	1,000	4,000	75	7.3	
6	2,000	0	500	2,500	80	7.8	9.4
7	2,500	0	700	3,200	78	11.2	60.4%
8	3,500	0	1,100	4,600	76	11.2	
Average	2,300	375	1,194	3,869	59	8.2	48.4%

through the hysterectomy. If the blood and blood substitutes are considered together, it will be observed that the volumes of such fluids employed varied from 1,500 c.c. to 4,400 c.c. with an average of 2,675 c.c. for each patient (Table II). Two principles have determined the amount of blood that should be administered to these patients: First enough blood should be given to secure the desired result; namely, to retrieve patients from shock or prevent its occurrence until obstetric hemostasis is attained and there is no further danger of loss of blood. Second, it is better that patients are not left with a severe anemia early in the puerperium. Barker and others[1] have shown that the risk of thrombophlebitis and fatal or nonfatal embolus after hysterectomy is more than four times as great for anemic patients as for those who are not suffering from anemia. Recently, we have tried to give enough blood so that the concentration of hemoglobin will be maintained at about 10 Gm. per 100 c.c. of blood. It is better to avoid administration of huge volumes of solutions of dextrose and saline when large volumes of blood are being given to replace fairly adequately the blood that has been lost. Solutions of saline or glucose are employed for the immediate intravenous transfusion during the few minutes that are required to obtain blood from the blood bank because they are as effective at this stage as blood and the efficiency of flow is easy to observe. From 100 to 200 c.c. of these watery solutions are administered rather rapidly and the remainder of from 500 to 1,500 c.c. is allowed to follow the blood at a slow rate. The volumes of intravenous fluids administered and the concentrations of hemoglobin in the blood after operation are shown in Table II. The cases are listed in chronologic order in this table.

Cases such as these challenge the judgment and skill of the obstetrician and test his capacity to act quickly and effectively. Instances of such severe hemorrhage are rare in general obstetric practice. However, in the small group of cases in which such severe hemorrhages

do occur, risk of death from exsanguination is exceedingly high. Because of this, such patients contribute heavily to the low maternal mortality rate in regions where the level of obstetric practice is high. In regions where the obstetric environment is less favorable, deaths from these hemorrhages also contribute noticeably to an already unfavorable maternal mortality rate. Laparotomy and repair, or removal of the uterus is the first obstetric treatment to be applied for rupture of the uterus. For other types of intractable obstetric hemorrhages laparotomy is, in a sense, a last resort but it should not be delayed too long.

The purpose of this paper is not to urge the frequent use of hysterectomy in the treatment of obstetric hemorrhage, but to point out its important place in the reduction of maternal mortality from exsanguinating hemorrhage when it *is* indicated. The operation is indicated when the uterus is the site of a lesion provocative of tremendous hemorrhage that is not accessible for hemostasis vaginally. Hysterectomy also is indicated when the usual methods of obstetric hemostasis, such as proper uterine tamponade through the vagina, fail. Once the indication has arisen, the operation should not be delayed, for in many instances such delay proves fatal. Removal of the uterus should be kept in mind as a lifesaving procedure for the type of patient whose cases are reported herein, and as such, it is not too radical a procedure. There is a natural reluctance to deprive any woman in the childbearing years of a normal uterus, but in the cases under discussion, the uteri were diseased and because of the lesion present, the life of the patient was acutely threatened from massive hemorrhage. Incidentally, this type of hemorrhage occurs much more commonly in multiparas than in nulliparas. In the eight cases reported, only one patient did not have a surviving child after hysterectomy and the group of eight mothers had twenty-one living children.

Summary

Eight cases of massive obstetric hemorrhage are reported that have been treated by hysterectomy. They occurred among 5,620 deliveries during a period of nine years. The fetal mortality was 50 per cent and there were no maternal deaths. Large volumes of blood and other fluids suitable for replacements were needed to sustain these patients through their hemorrhages and the operation of hysterectomy.

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THE USE OF A NEW CONTRAST MEDIUM (VISCO-RAYOPAKE) IN THE FEMALE GENERATIVE TRACT

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THE etiologic diagnosis of continued uterine bleeding presents a challenge to the clinician. It is often very difficult to determine whether such bleeding is endocrine or mechanical in origin. Obviously, a correct diagnosis is essential to the proper therapeutic management of the patient. Strangely enough, it is sometimes easier to make a diagnosis of an endocrine dysfunction as the basis for abnormal uterine bleeding than to determine the presence of a polyp or submucosal myoma which may be responsible for the symptoms. It is a recognized fact that simple curettage of the endometrium is not reliable in ascertaining the possible presence or absence of a small polyp or fibromyoma. Furthermore, it is equally as important to determine whether or not a large, palpable fibroid extends through the uterine wall into the endometrium. Such a tumor may or may not be responsible for the patient's symptoms, depending upon its degree of infringement, if any, upon the uterine canal.

The two methods which are available to the clinician in diagnosing the presence of an intrauterine growth, or to determine whether a large subserosal fibroid is the causative factor of bleeding are: (1) direct vision, and (2) the injection of a radiopaque substance directly into the uterine canal. The direct vision method is technically difficult and objectionable in that only the operator, and perhaps an assistant or two, can visualize the interior of the organ. Furthermore, there is no easily obtainable permanent record with this method, other than the memory of the operator, inasmuch as intrauterine photography is still an experimental procedure, the cost of which is prohibitive save for research purposes.

The radiopaque substance method of visualizing the interior of the uterus is far more practicable and has numerous advantages. Rindfleisch[1] was the first to make clinical use of this method less than 35 years previously. Several years later, Rubin[2] and others[3, 4] employed silver salts for this purpose. This was followed shortly thereafter by the halogens,[5-7] which were practically replaced by iodized oils in 1922.[8]

The so-called iodized oils have been used extensively and with remarkably good results for many years, but they are not without their objectionable features. An oil, regardless of its source, has a definite tendency to become stagnant in small channels and crevices. All too frequently a foreign body reaction will occur, giving rise to strictures of the narrower portions of the female generative tract. Such constrictions

are particularly prone to occur in the uterine tubes, and if the constriction is of such a degree as to occlude the tubes completely, sterility ensues. With any degree of constriction, however, the chances for the successful implantation of the fertilized ovum are markedly lessened. Another objection to iodized oils (poppy seed oil is the medium of one of the commonly used preparations) is that absorption of the substance from the generative tract is extremely slow, and it is not rare to find by means of roentgenography sizable amounts of oil even several months or years after it was placed there.

Obviously then, these substances are not ideal for hysterography. Rubin[9] lists the prerequisites of an ideal radiopaque contrast medium as follows: (1) adequate radiopacity; (2) rapid absorbability; (3) freedom from chemical irritation; and (4) proper viscosity. One of the most recent preparations which closely approximates the ideals listed above is Visco-Rayopake.* This product may be defined as a radiopaque contrast medium containing an organic iodine compound (2,4-dioxo-3-iodo-6-methyl tetra hydropyridine acetic acid) and a polymeric form of polyvinyl alcohol. The latter substance renders the compound viscous. Rubin[9] cites evidence to show the low toxicity of the drug. Since 3 Gm. per kg. of the contrast acid and 2 Gm. per kg. of polyvinyl alcohol given intravenously are well tolerated, the comparatively small relative amounts of the two substances (0.16 Gm. per kg. and 0.01 Gm. per kg.) received by the average patient could hardly be expected to give rise to toxic symptoms.

Methods

Visco-Rayopake may be injected directly into the uterine canal through the cervical opening, immediately following which roentgenographic studies are made, or the preparation may be introduced into a rubber bag or balloon which has previously been placed in the uterine cavity. Each of these methods has definite indications. In the small, shallow uterine cavity it is probably preferable to instill the contrast medium directly into the uterine canal through the cervix, as is common practice in the case of salpingograms. In the previously curetted uterus we prefer to insert a medium-sized de Pezzer catheter through the cervical canal with the aid of a uterine probe, then pulling the catheter down against the internal os as far as possible. Little or no leakage in the vagina occurs. This method is eminently more satisfactory than that of inserting a cannula, for it is almost impossible to prevent leaking of the medium around the instrument into the vaginal vault. We then instill the dye under low pressure until the patient complains of mild abdominal discomfort. The catheter is clamped and anteroposterior roentgenograms are taken immediately. These are followed by lateral and postero-anterior views. The latter are important in visualizing certain small polyps or submucosal myomas. As soon as the roentgenograms have been obtained, the substance is allowed to escape from the external end of the catheter. Remarkably little of the contrast medium is ever found in the uterine tubes, and the preparation rarely escapes into the abdominal cavity.

*An experimental preparation, kindly supplied through the courtesy of Dr. William T. Strauss of Hoffmann-La Roche, Inc., Nutley 10, N. J.

In those patients who have profuse bleeding and a small canal, we have found it better to perform a preliminary curettage. It is believed this procedure is necessary to prevent forcing potentially infected blood into the uterine tubes where a secondary infection may be induced.

If the uterine cavity is believed to be large, we prefer to insert a small rubber balloon into the organ and instill the Visco-Rayopake into the former. The canal is thereby well outlined, for a protruding polyp or submucosal fibroid will cause a depression of the balloon. The entire procedure is carried out under general anesthesia. Originally we found that the patient would often expel the balloon during recovery from the anesthesia, and we, therefore, attached a small de Pezzer catheter to the neck of the balloon, proceeding to introduce it as previously outlined. Six to ten c.c. of water are allowed to gravitate into the balloon before the patient leaves the operating room in order to make certain that the apparatus is in good position. The remainder of the procedure is quite similar to the no-balloon method described above.

If the patient has had rather profuse bleeding, it is customary to allow the balloon, inflated with air, to remain in situ following the taking of roentgenograms for a varying period of time. The balloon thus acts as a hemostatic agent, and is more desirable than packing the uterine cavity with gauze. Deflation and removal of the balloon can usually be performed within 24 to 72 hours.

Case Reports

To date, we have studied the generative tracts of some 20 patients having various gynecologic complaints. In every instance Visco-Rayopake has been found to outline the desired parts with clarity and sharp demarcation. There have been no reactions of any kind, and in the great majority of cases there was no roentgenologic evidence of any traces of the contrast substance in films taken about one hour after the material was allowed to drain from the internal genitalia.

So as to illustrate some of the varied type of cases to which Visco-Rayopake is applicable, we present below a few representative reports.

Case 1.—C. J., a 26-year-old Negress, complained of severe dysmenorrhea and occasional intermenstrual spotting. For the past 2 or 3 years, despite normal menstrual period intervals and duration, she experienced distressing uterine cramps and pelvic discomfort during each entire period. The spotting was more pronounced and prevalent for the 3 months prior to examination. During menstruation the pain was most severe in the left lower abdominal quadrant, and persisted to a lesser degree for 7 to 10 days after the flow had stopped. There were no associated urinary or gastrointestinal symptoms.

Examination revealed a well-developed and well-nourished young adult Negress. The head, neck, chest and abdomen presented no abnormalities. Pelvic examination revealed a normal introitus; the vaginal mucosa was normal as was the cervix from which a small amount of blood was oozing. The uterus was in good position, and there were no masses palpated in the fornices although the left fornix was slightly tender.

Because of the pain and tenderness in the left lower quadrant in addition to the severe dysmenorrhea, the patient was advised to undergo

hysterography followed by a dilatation and curettage of the uterus. Due to the fact that the patient also had fairly frequent episodes of spoting, it was deemed advisable to insert a de Pezzer catheter prior to the Visco-Rayopake instillation in order to obtain roentgenograms from different angles which would be useful in visualizing a polyp or submucosal myoma.

Fig. 1.—X-ray of the uterine canal and Fallopian tubes after injection with Visco-Rayopake.

Therefore, under gas anesthesia the cervix was dilated and endometrial scrapings obtained for laboratory examination. Following this a medium-sized de Pezzer catheter was inserted beyond the internal os. When the patient had recovered from the effects of the anesthetic, ten c.c. of Visco-Rayopake were instilled into the uterine cavity through the catheter. Several roentgenograms taken almost immediately thereafter revealed no evidence of any polyp or submucosal myoma. However, the substance failed to enter the left tube. On the basis of this finding, an exploratory laparotomy was advised for disease in the left adnexa.

This case illustrates the manner in which Visco-Rayopake may be used to diagnose tubal obstructions.

CASE 2.—D. L., a 30-year-old white female, complained of being unable to conceive. The family history revealed nothing of particular interest. Menses began at the age of 14, recurred every 28 days, and lasted 3 to 4 days. The past history was irrelevant.

Fig. 2.—Same as Fig. 1, in another case.

For the past five years, the patient had attempted to become pregnant. The husband presented no immediately discernible abnormalities, and the patient was referred to us for a complete gynecologic investigation.

Physical examination revealed nothing abnormal. The introitus was of the marital type, vagina and cervix were normal, and the uterus of average size in normal position. The fornices were nontender and presented no masses.

Laboratory examination of the blood and urine showed no abnormalities.

Accordingly, uterosalpingography with Visco-Rayopake was decided upon and 10 c.c. thereof instilled into the uterine cavity. Roentgenograms revealed normal outlines, the substance readily entered the uterine tubes. Ninety minutes thereafter, a hysterosalpingogram revealed no traces of Visco-Rayopake. An endometrial biopsy proved to be normal, and the patient's husband was referred to a urologist for sperm analysis.

This case illustrates how Visco-Rayopake can prove valuable in investigating the patency of the uterine tubes in a woman suspected of being sterile.

CASE 3.—C. F., a 26-year-old white married woman, complained of frequent menses with some spotting between periods. The patient had been married 8 years with no pregnancies. Menses had started at the age of 14, and had never been regular. She had had a dilatation and curettage of the uterus performed at the age of 16, but relief had been obtained for only 6 months.

During the past 3 or 4 months, the periods occurred every 14 to 21 days and lasted for 5 or 6 days. No other positive findings were elicited save for a 10-pound gain in weight in the past 18 months, and a history of considerable intolerance to cold weather.

Physical examination revealed no abnormalities of the head, chest or abdomen. The vaginal introitus and mucosa were normal. There was a considerable amount of blood flowing from the cervix, which was not eroded. The uterus was of average size, in good position and freely movable, and the fornices clear.

Laboratory examination revealed essentially normal blood and urine analyses.

In view of the distinct possibilities of an intrauterine or small submucosal polyp, it was deemed advisable to have the patient undergo hysterography. Ten c.c. of Visco-Rayopake were instilled and the succeeding roentgenograms revealed some irregularity of the uterine canal, which however, was not definite enough to allow us to make an unqualified diagnosis of a polyp. None of the substance entered the uterine tubes.

A basal metabolic rate determination was reported as minus 22 per cent. Following 3 months of thyroid medication, the patient reported that she had had no uterine bleeding for one month; she was definitely improved and "felt fine."

This case is typical of the type where it is essential to know whether the bleeding is of organic or of endocrine origin.

CASE 4.—M. K., a 46-year-old woman, complained of increasing frequency of the menses associated with excessive bleeding and spotting between periods. The past history was irrelevant. Menstruation had been normal up until one year previously. There had been some weight gain, but nothing remarkable.

Physical examination revealed a normal head, chest and abdomen. The vulva, vagina and cervix presented no abnormalities. The uterus was somewhat enlarged, and multiple fibroid-like masses could be felt on the corpus. The fornices were clear.

In order to rule out the possibility of the uterine masses extending through to the mucosa and causing the profuse menstrual bleeding as well as the spotting, it was decided to instill 10 c.c. Visco-Rayopake into the uterus and then obtain hysterograms. This procedure revealed no irregularities, and subsequent curettings were reported as normal.

Following the administration of thyroid extract given because of a low metabolic rate, the menses became regular and menorrhagia and spotting ceased.

This is an example of a case where uterine fibroids existed in the presence of menstrual disturbances. Visco-Rayopake proved valuable in ruling out the organic lesion as the primary causative factor.

Fig. 3.—X-ray taken one hour after injection, showing rapid absorption of the dye.

CASE 5.—V. P., a 32-year-old white married female, complained of lower abdominal pain of 2 years' duration. Her menses began at 14, had always been regular and lasted 4 to 5 days. For the past 2 years she had experienced dull, aching pain across the lower abdomen, more pronounced on the left, occurring during the menses, and more recently between periods as well. The pain was sometimes of such severity as to require the patient to stay in bed 2 or 3 days at a time.

Physical examination revealed no abnormalities except slight tenderness over the lower abdomen, and a partially fixed uterus with tenderness and an indefinite mass in the left fornix.

It was believed that the patient had an ovarian cyst. Prior to surgical intervention, 10 c.c. Visco-Rayopake were instilled into the body of the uterus by cannula (the patient was nulliparous and the uterine canal believed to be shallow). Hysterography showed the uterus to be pulled or pushed markedly over to the left, and the left uterine tube greatly dilated.

At operation the left tube and ovary were found closely adherent to the uterine body. The left ovary was almost completely replaced by a large cyst.

This case illustrates how Visco-Rayopake can serve as an aid in the diagnosis of disease of the uterine adnexa.

Discussion

The case reports cited here are but a few examples of the instances in which the use of hysterosalpingography is essential to the intelligent management of the patient. Heretofore, one might well hesitate to undertake such a measure because of the inherent toxicity and delayed reactions of the available products. However, with the advent of relatively nontoxic, rapidly absorbed dyes such as Visco-Rayopake, the procedure becomes more readily adaptable to routine use.

The technique which we use is simple and consists merely of the shaving and cleansing of the vulva, application of an antiseptic, followed by instillation of the medium with the patient in the lithotomy position. The entire procedure can be carried out in the x-ray room, and the patient can, in the uncomplicated cases, usually be ambulatory. In no instance did we ever note a reaction of any type from the Visco-Rayopake which was rapidly absorbed from the tissues, often within 60 minutes. In our opinion, there is no longer any place for an oily contrast medium for hysterosalpingograms.

We believe that every patient with a suspected uterine or tubal obstruction can and should be thus examined, and we foresee the day when hysterosalpingography will be a routine procedure in gynecologic examinations.

I desire to acknowledge the assistance and cooperation of Dr. B. E. Rhudy, roentgenologist, Greensboro, N. C.

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ADENOACANTHOMA OF UTERUS

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ADENOACANTHOMA or squamous metaplasia, in association with adenocarcinoma of the endometrium, is a rare form of malignancy. Healy and Cutler[1] found only three out of one hundred cases of fundal carcinoma. Novak[2] states that the tumor is of a low degree of malignancy (Grades 1 and 2) growing slowly and metastasizing late. This opinion would not appear to be universal, however, as Meigs[3] places it midway between cervical and fundal carcinoma in malignancy, and he states that metastasis is rapid and widespread.

The microscopic picture is unusual and variable. Frequently, the pattern found is that of an adenocarcinoma with islands of squamous epithelium scattered among the glands, lying free in the stroma or sometimes in the glands themselves. The origin of this ectopic squamous tissue has been the subject of much discussion. The view that it is a combination malignancy has been generally abandoned. In general, a malignant growth tends to reproduce in a disorderly embryonic fashion the pattern of the epithelium from which it arises. Novak[2] states that the origin is from certain "indifferent" cells beneath the normal columnar uterine epithelium, these cells possessing a differentiating potency which, under certain circumstances, can lead to the formation of squamous epithelium.

In some benign conditions, especially inflammatory lesions, squamous metaplasia may occur in the uterus, just as it occurs in the endocervix in cervical erosions. Chronic irritation in the uterine cavity might likewise cause a similar metaplasia. It is known that benign metaplasia does occur in certain cases of endometritis. Zellar[4] has presented evidence of the effect of chemical irritants on the uterine epithelium. In 1885, he reported 63 cases of chronic endometritis showing squamous metaplasia following long-continued intrauterine application of iodine, bichloride of mercury or carbolic acid. Novak[2] states that he has seen no instance in which metaplastic areas revealed any indication of malignancy, though admitting that this might occur.

This tumor responds poorly to radium, and total hysterectomy and removal of the ovaries and tubes is the treatment of choice providing evidence of metastasis is not present.

Case Report

The patient was a 56-year-old female of French-Canadian extraction, who was admitted to the hospital complaining of irregular vaginal hemorrhages. When first seen in October, 1941, she had been bleeding continuously for six weeks and was suffering from weakness due to loss of blood. Her menstrual history was unusual in that at the age of 36 years, following the birth of her last child, she had a period of irregular menstruation extending over fifteen years, up to the time when the patient presented herself for examination. At times, her bleeding

would persist for several weeks continuously to be followed by periods of amenorrhea of two to three months' duration. For four months prior to her admission to the hospital, however, the bleeding had been continuous increasing at times to the proportion of a severe hemorrhage. It is of interest to note that this hemorrhagic condition accompanied an emotional upset caused by the fatal illness of her husband, and the capture and imprisonment of her son who is serving with the Royal Canadian Air Force overseas.

Fig. 1.—Showing atypical cystic glands with an island of benign-appearing squamous tissue intimately associated with the gland epithelium.

Examination revealed an obese female, who appeared anemic and weak. The blood pressure was 160/90 and the blood sugar investigation showed a latent diabetes with intermittent glycosuria. On pelvic examination, it was found that there was an almost complete upper vaginal stenosis obscuring the cervix to visual examination. This structure could be palpably defined as a small, firm, mobile organ attached to a hard, symmetrically enlarged uterus about the size of a two months' pregnancy. The uterus was quite mobile and the broad ligaments were free of palpable exudate or fixation. The adnexa could not be felt.

A laparotomy was performed, and the uterus was found to be very large and very firm, freely movable with a small cervix suspended in a mobile broad ligamentary hammock. The right adnexa appeared normal except for tubal thickening, but the left tube and ovary were only represented by a vestigial-appearing nodule the size of an olive, adherent to the round ligament and the posterior wall of the uterus. A panhysterectomy was performed, the broad ligaments and the pelvic floor being left palpably free of any glands or thickening. The patient made an uneventful recovery.

Pathologic Report.—Gross examination of the uterus revealed a fundus about the size of a baseball, uniformly symmetrical, attached to a small but elongated cervix. The uterus felt very hard and cut with

a dense leathery consistency. The uterine wall was 5 to 6 cm. thick with numerous loculi communicating with an irregularly enlarged uterine cavity. The cut section presented a uterine cavity shaped somewhat like a bunch of grapes with some of the branches extending far out into the myometrium. Surrounding each pocket the tissue appeared to be almost rock-hard, cutting only with extreme difficulty. The center of the uterine cavity showed some areas of ulceration.

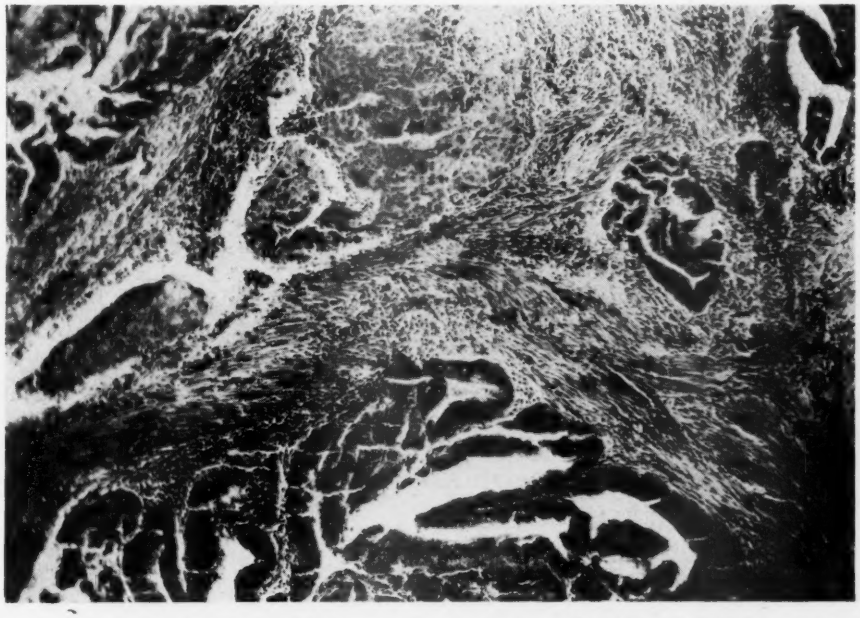

Fig. 2.—Adenocarcinomatous glands and islands of malignant-appearing squamous tissue isolated in the stroma. Note extensive exudative reaction.

Microscopic examination revealed an unusual picture with many large endometrial glands presenting a hyperplastic appearance. In certain areas, however, the glands showed definite adenocarcinomatous changes (Fig. 2). Other parts showed islands of squamous epithelium, some of these presenting a benign appearance (Fig. 1); while others showed malignant changes of the squamous carcinomatous type (Fig. 2) spreading extensively throughout the endometrium. The other pelvic tissues presented nothing remarkable, and showed no evidence of metastasis.

Comment

The occurrence of two types of malignancy, the usual adenocarcinoma of the endometrium and the unusual squamous carcinoma appearing side by side in the fundus of the uterus, presents an extremely uncommon and interesting picture.

The microscopic picture presented would appear to favor stromal metaplastic origin for the ectopic squamous tissue, some islands appearing in glands while others appear isolated in the stroma away from any glandular epithelium. The finding of the epithelial pearl formation and squamous tissue showing embryonic characteristics in this case indicates that growth activity of a malignant type may occur in these squamous islands.

It would appear that we were fortunate enough to remove the pelvic organs before any metastasis had occurred. It is now three years since the operation. The patient is enjoying good health, and shows no evidence of recurrence or metastasis. Therefore, she should have a good chance of being entirely cured.

Summary

A case of adenoacanthoma of the uterus has been presented in which there is evidence of malignant change in the squamous tissue as well as in the glandular.

Brief references have been made to the literature.

The microscopic picture in this case would appear to favor stromal metaplasia as the origin of the abnormally placed squamous tissue.

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CYSTIC PELVIC CHORDOMA SIMULATING AN OVARIAN CYST

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CYSTIC pelvic chordoma is a rare and interesting condition, and since it presents an additional entity in the differential diagnosis of cystic pelvic masses, we felt it worth while reporting.

Chordoma is a tumor which originates in the remnants of the notochord. According to Delafield and Prudden,[1] in man it is a transient, though important, embryologic structure which disappears early in fetal life except for traces remaining in the intervertebral discs (nucleus pulposus). The histopathologic picture is one of large vacuolated cells with smaller cytoplasm, lying in a homogeneous or finely granulated, jellylike matrix; these elements readily break down, leaving empty spaces in the intercellular material.

Chordomas may occur anywhere along the spinal cord, or develop from the sacrum and coccyx. Both benign and malignant growths have been described in the sacrum.[2, 3]

In a very thorough and extensive review of the literature, and their personal cases, Stewart and Morin[4] have shown that chordoma was described by Müller in 1858 for the first time; and confirmed and corroborated by Ribbert in 1894, as a distinct pathologic neoplasm. The French pathologists, too, took up the new notochord neoplasm and in 1914, Alezais and Peyron have shown and described the pathogenesis and histogenesis of the chordoma. The German literature also described cases of chordoma but none simulating an ovarian cyst. The English literature began to present cases of chordoma in the early part of 1920; and again up to 1926, Stewart and Morin reported 25 cases of chordoma in spheno-occipital area and 27 cases of sacrococcygeal region.

Rane and Riss of Paris, 1924, saw a case in the lumbar region between the fourth and fifth vertebrae. Other reports have shown cases in the lower dorsal region. Since 1858, when Müller first described chordoma and up to the present time, none of the reported cases has been so located as to present a gynecologic problem.

The morbid anatomy, according to the experiences of Stewart and Morin, varies. Clinically, the degree of mucoid degeneration present in a chordoma is an index of its comparative benignancy. The formation of mucin being in inverse ratio to the rate of cellular activity. With increasing malignancy, the tumor becomes more and more solid and opaque. One of the most striking features of the chordoma is its locally destructive effects on bone.

Chordoma is usually a tumor of low malignancy, slowly infiltrating and destructive; tends to recur after removal; exceptionally, it may metastasize.

Of the various cases reported by Stewart and Morin the age groups were as follows:

34.9 years in the 20 cases of the spheno-occipital region.
50.6 years in the sacrococcygeal cases; the youngest being 16 years, while the oldest was 72 years.
Males were in the ratio of 2:1.

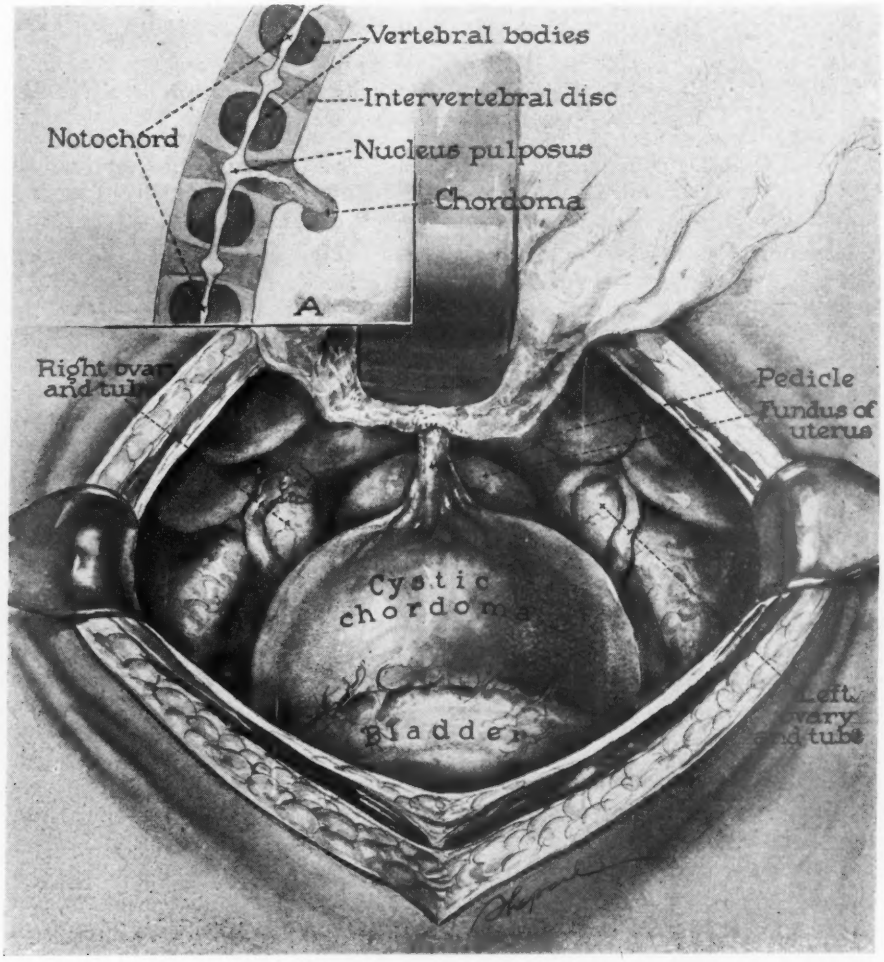

Fig. 1.—Cystic chordoma as seen during laparotomy.

Case Report

C-44-9715—D. J., aged 20 years, Negro woman, married, was admitted to the gynecologic ward of the Cook County Hospital on 3/7/44.

Complaint: Menorrhagia for 2 years. Patient stated that during her last postpartum examination in May, 1942, she was informed of the presence of a tumor on her "womb." Since the birth of her child, she noticed that her menses became "longer and heavier," using about 14 pads daily.

Began to menstruate at 15 years of age; regularly every 29 days; she had no pain with her menses.

She is gravida i, para i, and was delivered April, 1942, normally, spontaneously of a full-term baby. The remaining history is essentially negative except for hay fever for the last 5 years.

Physical examination revealed a young Negro woman who was not acutely ill. She is intelligent and cooperative. Head, neck, heart, lungs and upper abdomen failed to reveal any gross pathologic findings.

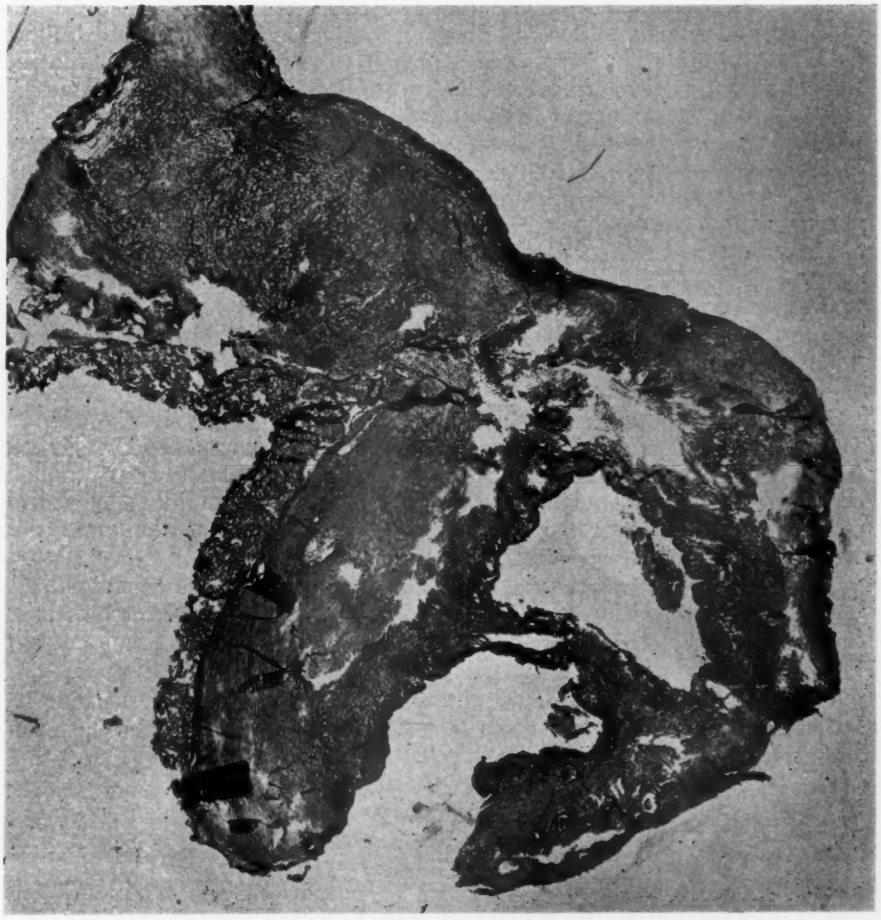

Fig. 2.—Section of cystic chordoma. (×90.)

Lower abdomen revealed the presence of a mass which was distinctly cystic, smooth, regular, and spherical, which extended up to the umbilicus. There was no rigidity, no specific areas of tenderness upon palpation. Inguinal adenopathy was absent.

Urethra, Skene's and Bartholin's glands were not diseased.

The patient was catheterized prior to pelvic examination.

Cervix was free, lacerated and pointed upward toward the symphysis.

Corpus uteri was small, firm, symmetrical and retroverted.

There was a large cystic mass which was prominently felt in the anterior aspect of the pelvis in the midline extending up to the umbilicus.

Rectally, the afore-mentioned findings were confirmed.

The impression was that of an ovarian cyst.

Laboratory findings were:

Hb. = 80%
R.B.C. = 4,100,000
W.B.C. = 8,600
Urine was negative for albumin and sugar.

Laparotomy findings: A large cystic mass measuring the size of a normal fetal head, filling the lower pelvis, was located between the bladder and uterus and was adherent to the former by an old inflammatory process. The mass was attached to a long pedicle, simulating the umbilical cord of a newborn baby, the latter passed over the mesentery to the dorsal spine. The cystic neoplasm had a thick capsule measuring approximately 1/8 of an inch; it was of whitish-gray glistening hue. Many vessels coursed over this mass. When cut, sebaceous, greasy, yellowish-green substance ran out. The uterus was of normal size, firm and retrodisplaced in the cul-de-sac. Both ovaries were intact, slightly flattened and cystic, but no gross abnormalities. The tubes were congested, but free. The fimbriae were free and the tubal ostia were patent.

The mass was removed by separating it from the bladder adhesions and the pedicle was cut and transfixed as close to the lower dorsal spine as was accessible. The abdomen was closed in layers.

Pathological Report: Specimen.—Cyst had been previously opened, measuring approximately 12 cm. in diameter. Adherent to the surface are numerous fibrous adhesions. In one area on the surface are numerous 1 mm. in diameter vesicles filled with reddish fluid. The lining is green and tan covered with yellowish-white, thick purulent material. In some areas, the cyst wall is thinner and coarsely trabeculated.

Microscopic sections show areas consisting of large vesicular cells with bluish staining basophilic cystoplasm. Also present are connective tissue and many thin-walled blood vessels. Portions of tissue contain large accumulation of lymph.

Diagnosis: Chordoma, with superimposed inflammatory reaction.

This patient had an uneventful convalescence and was sent home on the eleventh postoperative day.

Summary

We present a neoplasm which originated in the lower dorsal spine, but migrated to the pelvis by virtue of a long pedicle. Its presence in the pelvis simulated an ovarian cyst.

Only by careful microscopic sections did the diagnosis of chordoma become apparent.

In going through the literature we failed to find any other case of similar pelvic location.

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PREGNANCY COMPLICATED BY ADDISON'S DISEASE*

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ADRENAL insufficiency in its various forms has been much discussed in literature since the initial description of the disease by Addison. Etiological factors other than tuberculosis have been recognized with a more critical analysis of pathologic changes precipitating the condition. The advent of hormonal therapy and the development of synthetic preparations have done much to prolong the lives of individuals afflicted with adrenal insufficiency.

In 1922, Gilbert Fitzpatrick[1] first reported in American medical literature a case of Addison's disease complicated by pregnancy. A careful review of all literature by him revealed eleven cases in which pregnancy and Addison's disease had coexisted. The majority of the case histories were sketchy and inconclusive, but two facts were obvious. First, that all cases died during pregnancy or shortly after delivery. Second, that the fetal prognosis was good when the pregnancy advanced to term. Fitzpatrick reported the twelfth case in which acute adrenal insufficiency developed twenty hours after delivery. The patient was treated with adrenalin and thyroid extract with survival for at least one year after the onset of the disease.

In the October 29, 1932, issue of the *Journal of the American Medical Association,* Percy A. Perkins[2] reported the thirteenth case of Addison's disease and pregnancy, stating in this article that no case had previously survived. There was a failure to mention the case reported by Fitzpatrick ten years previously. Perkin's case was a para-three, the third pregnancy occurring five years after the onset of Addison's disease. For one year prior to delivery, the patient had taken a cortical hormone preparation orally and she delivered normally with no postpartum complications. The author was impressed by the fact that the patient seemed subjectively improved by the pregnancy.

In the foregoing cases, the benefit of a more complete study by various chloride excretion tests was lacking. In addition, the several types of hormonal therapy more recently developed could not be evaluated. It is our purpose to report a case of pregnancy complicated by Addison's disease of fourteen months' duration, which has recently been studied in the Family Outpatient Dispensary at the Naval Hospital in Philadelphia.

The patient, a primigravida, twenty-eight years of age, reported to the Prenatal Clinic on February 4, 1944. Her last menstrual period had occurred on July 4, 1943, and her expected date of confinement was April 11, 1944. She had been ambulatory during the first seven months of pregnancy, but complained of progressive weakness and a persistent deepening of the previously existing pigmentation. She had been re-

*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

ceiving small doses of extract of adrenal cortex hypodermically. The patient's general health had always been good and she had dated the onset, of what had been diagnosed Addison's disease, to the end of April, 1942. Three weeks previously, the patient had given blood to the Red Cross. This had been followed by marked asthenia, necessitating bed rest for three weeks, at the end of which period, the pigmentation was first noted about the face. The asthenia and pigmentation advanced quite rapidly, and it became necessary for the patient to relinquish her position as a dietitian. The pigmentation had been definitely accentuated by the pregnancy.

The husband was on active duty in the Navy and was well. The mother had died of carcinoma of the rectum. The father, one sister, and two brothers were living and well. The sister, who accompanied the patient to the clinic, was fair-complected and volunteered the information that before the initial pigmentation, their skins had been of equal fairness.

The patient was of slight build, appeared somewhat lethargic, and showed a striking bronze pigmentation of the entire body, with a deeper pigmentation of the face, hands, areolae, vulva, and thighs. The gums and hard palate were studded with accumulations of pigment that were deep brown to black. The blood pressure was 100/70. The patient was considered to have a small gynecoid pelvis, and it was felt that delivery could be completed vaginally.

Skull plates showed no bone changes, and there was no x-ray evidence of any disease process in the lungs. The heart measurements were considered normal for size and configuration. Stereoscopic plates and serial studies of the adrenal areas revealed no abnormal calcification. Ophthalmoscopic examination showed no eye-ground changes. Urinalysis was negative. Kahn and tuberculin tests were negative. There was a moderate degree of hypochromic anemia.

The patient was admitted to the hospital on February 24, for chloride excretion tests for adrenal insufficiency. The reports were as follows:

Blood plasma:	No. 1 (8 A.M., 2nd day)		584 mg. % NaCl
	No. 2 (10 A.M., 3rd day)		524 mg. % NaCl
Urine specimens:	No. 1 (8 A.M. to 8 P.M., 2nd day)	840 c.c.	330 mg. % NaCl
	No. 2 (8 P.M. to 8 A.M., 3rd day)	1,180 c.c.	240 mg. % NaCl
	No. 3 (8 A.M. to noon, 3rd day)	60 c.c.	550 mg. % NaCl

Interpretation: (According to Cutler, H. H., Powers, M. H., and Wilder, R. M., Proc. Staff Meetings, Mayo Clinic **13**: 244, 1938.) If the concentration of chloride in the third-day specimen of urine is above 225 mg. per cent, Addison's disease or adrenal insufficiency is strongly suggested, and if it is less than 125 mg. per cent Addison's disease is unlikely. Plasma chloride will nearly always fall below 550 mg. per cent in Addison's disease on the third-day blood specimen.

The patient was placed on a high protein, high carbohydrate, high salt, low potassium diet and this was augmented by two grams of sodium chloride in tablet form and two c.c. of eschatin twice a day. She was given ferrous sulfate, calcium lactate, and thiamin chloride in addition to the prescribed diet. Her weight-gain had been but moderate, and she was carefully observed for any signs of fluid retention. Asthenia remained constant; the pigmentation showed a gradual deepening, and the blood pressure remained consistently low.

The first admission to the maternity floor was on April 12, 1944, at which time actual labor had not begun and the patient was discharged. She was readmitted at 5 A.M. on April 20. The membranes had ruptured five hours previously. Labor began seventeen hours later, and was terminated by an outlet forceps delivery of a normal male infant at 10:45 A.M., April 21. There was an estimated blood loss of 250 cubic centimeters. The patient was given 1,000 c.c. of normal saline before she left the delivery room.

Eschatin was continued in 5 c.c. doses twice daily, and the previous diet continued. The patient was comfortable until the third postpartum day, when there was a moderate temperature elevation, marked weakness, and nausea. Additional amounts of eschatin and sodium chloride were administered and on April 29, 500 c.c. of whole blood were given. In cross-matching, the materials were incubated for a period of one hour, no Rh– serum being available. The highest blood pressure recorded on the third postpartum day was 108/70, and the lowest on the seventh postpartum day was 76/48. Chloride excretion tests carried out on the twelfth postpartum day were unreliable because of the failure to adhere to a measured salt intake and the neglect in the administration of potassium citrate to displace the sodium radical. A single plasma chloride determination completed on the baby was 570 mg. per cent. The patient was discharged from the hospital on the sixteenth postpartum day at which time her condition was splendid.

An additional chloride excretion test was performed at the hospital on June 22, 1944, two months after delivery. The patient had been unable to obtain eschatin, and accordingly had received none for a period of two weeks. She had adhered to a high chloride, high carbohydrate, high protein, low potassium diet, and had in addition taken three grams of sodium chloride daily in tablet form. Her weight had remained constant. There had been no appreciable change in pigmentation, but there had been a rather marked general weakness. The systolic blood pressure readings during the three days of hospitalization had remained consistently below 90. The patient was placed on a fixed diet. The chloride excretion tests were as follows:

Blood specimens:	No. 1 (8 A.M., 2nd day)		562 mg. % NaCl
	No. 2 (10 A.M., 3rd day)		556 mg. % NaCl
Urine specimens:	No. 1 (8 A.M. to 8 P.M., 2nd day)	600 c.c.	500 mg. % NaCl
	No. 2 (8 P.M. to 8 A.M., 3rd day)	610 c.c.	550 mg. % NaCl
	No. 3 (8 A.M. to noon, 3rd day)	150 c.c.	720 mg. % NaCl

(The concentration of chloride in urine in the third-day specimen is stated to be more accurate in diagnosis of adrenal insufficiency than is the concentration of sodium, potassium, or chloride in serum, the concentration of potassium in the urine, or total excretion of sodium, potassium or chloride.)

We feel that this patient represents a case of chronic adrenal insufficiency. This is borne out by the presence of asthenia, hypotension and characteristic pigmentation. Gastrointestinal symptoms were not conspicuous except for frequent spells of nausea. There is no history or roentgenologic evidence of tuberculosis as the precipitating factor. The one x-ray of the heart revealed no diminution in the size of the heart shadow. The chloride excretion tests on two occasions have been con-

clusive. Pregnancy has not affected the course of the disease to date. Adrenal cortex extract (eschatin) was administered because of its availability, and the fact that the patient was subjectively improved while receiving it. It is possible that the synthetic desoxycorticosterone has its advantages because of the better standardization of the preparation.

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AN INTRAGROUP HEMOLYTIC TRANSFUSION REACTION IN AN RH-POSITIVE PATIENT

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THE cause of *intragroup* hemolytic transfusion reactions in obstetrics became of great importance following the work of Wiener and Peters[1, 2] which implicated the Rh factor of Landsteiner and Wiener.[3, 4] It is now considered a fact that if a pregnant woman is Rh negative and if her fetus is Rh positive, the baby's blood may sensitize the mother and stimulate the production of Rh isoantibodies. At some subsequent time, if such a sensitized woman should be given a transfusion of Rh-positive blood and if the titer of anti-Rh isoantibodies in her body should be high enough, hemolysis of the donor's Rh-positive red blood cells will take place (even though the bloods are of the same blood group), giving rise to an intragroup hemolytic transfusion reaction. The same is true of certain nonpregnant individuals who are Rh negative and are given transfusions of Rh-positive blood. The first transfusion may sensitize the recipient, so that the blood of subsequent transfusions will be hemolyzed.

However, the problem is not so simple, for the Rh factor is not a single entity, but comprises at least five distinct varieties of Rh agglutinogens which have been designated Rh_0, Rh_1 (Rh_0'), Rh_2 (Rh_0''), Rh′, Rh″. These give rise genetically, to the following eight Rh types: Rh_0, and Rh_1, Rh_2, Rh_1Rh_2, Rh′, Rh″, Rh′Rh″ and Rh negative. The practical importance of this finding is that there are three principal varieties of anti-Rh sera: anti-Rh_0, anti-Rh′ and anti-Rh″; and unless all bloods are tested with all three types of sera, some Rh-positive bloods may be classified as Rh negative. Moreover, in rare cases, patients of one Rh type may be sensitized against blood of a different type; e.g., an individual who is Rh′ or Rh″ may be sensitized by blood of types Rh_1 or Rh_2. These facts are summarized in the papers by Wiener and his associates who first described the Rh types.[5, 6]

In addition, the subject has become even more complex since the discovery of the Hr (or St) factor,[7, 8] which is an antigen shared by bloods of several of the Rh types, namely, Rh-negative bloods, those containing properties Rh_2, Rh_0, and Rh″, and heterozygous Rh_1 and Rh′ bloods; while Hr is absent from homozygous Rh_1 and Rh′ bloods. The significant feature of this is that just as an Rh-negative individual may be sensitized against Rh-positive blood, so may an Hr-negative individual be sensitized against Hr-positive blood. Furthermore, an Hr-negative individual is always Rh positive. Therefore, one is not justified in feeling completely secure when transfusing an Rh-positive individual. This is seen from the case to be presented in which a transfusion reaction occurred in an Rh-positive individual, who was given Rh-negative blood, the reverse of the usual combination which causes trouble.

S. C., 26 years of age, white, gravida iv, para iii, term gestation, was admitted to the obstetrical service of Bellevue Hospital on June 2, 1944,

in active labor. Antepartum course had been uncomplicated. Her first two pregnancies, two and five years previously, ended in forceps deliveries, but were otherwise uneventful. In 1943, the patient had a normal spontaneous delivery which was complicated by a manual removal of the retained placenta and a blood loss of 850 cubic centimeters. The patient was transfused at that time with 500 c.c. of whole bank blood without any reaction.

Admission physical examination and laboratory work-up revealed nothing remarkable. After a first stage lasting 11 hours and 50 minutes and a second stage lasting 10 minutes, the patient was delivered spontaneously of an apparently normal male child weighing 5 pounds 9 ounces. The baby breathed and cried at once. The placenta remained attached to the uterus and after 1 hour and 23 minutes, it was expressed finally with a blood loss of approximately 1,400 cubic centimeters. One-third of the placenta was beefy red and did not contain normal-appearing cotyledons. The patient's blood pressure fell to 90/50 and she was given immediately 300 c.c. of plasma. Following this, her blood pressure returned to normal. About two hours after the placenta had been expressed, a transfusion of group AB apparently compatible (as determined by cross-matching) bank blood was started. This blood was only two days old. After the blood had been running 55 minutes and the patient had received almost 100 c.c., she suddenly began to vomit and had severe lumbar pain with a shaking chill. The transfusion was discontinued immediately, and an infusion of normal saline started. A sample of the patient's blood which had been taken before the transfusion was started, another sample drawn during the chill, and the donor's blood together with a sample of the baby's blood were sent to the Serological Laboratory of the Office of the Chief Medical Examiner which is under the direction of Dr. A. S. Wiener. The following were the findings:

	Group	*Rh Type*	*Hr*
Patient	A_1B	Rh_1	Negative
Donor	A_1B	Rh neg.	Positive
Baby	Not done	Rh_1Rh_2	Positive

Dr. Wiener's hypothesis to explain this intragroup incompatibility was that the patient had in her body anti-Hr isoantibodies which had been formed during her present pregnancy (or after her transfusion one year ago, or possibly both), having been sensitized by the Hr antigens in her baby's red blood cells. Thus, when she was transfused with Hr-positive blood hemolysis occurred. As already mentioned, the patient's blood taken during the chill showed definite hemolysis, the plasma being light orange in color.

To further test this hypothesis, Dr. Wiener performed a biologic test[9] on the patient. The patient was given 50 c.c. of Hr-negative blood* intravenously and one hour later, a sample of blood was withdrawn from the patient's vein. There was no clinical reaction and the plasma taken after the test was no darker than the control plasma obtained before the injection. The patient was then given 50 c.c. of Hr-positive blood.† Although the patient had no clinical reaction following this injection, a sample of blood taken from the patient's vein one hour later revealed definite though slight increase in the icteric index, and after a second hour the plasma was even darker, indicating definite hemolysis. Anti-Hr

*This blood belonged to group A_1, type Rh_1.

†This blood belonged to group A_2, type Rh_1 Rh_2.

isoagglutinins could not be demonstrated in the maternal serum, though tests were carried out periodically until one week post partum; but this absence of isoagglutinins occurs also not infrequently in Rh-negative mothers of erythroblastotic babies.

The baby was carefully observed for the possibility of developing erythroblastosis fetalis, but this did not occur. In fact, the infant's hemoglobin never dropped below 12 grams. Nevertheless, the infant was kept off the breast because of the possibility of anti-Hr isoantibodies passing out in the milk.

Summary

1. A case is reported in which the Hr factor appeared to be responsible for an intragroup hemolytic transfusion reaction.

2. The use of Rh-negative blood is not the complete answer for the prevention of intragroup hemolytic transfusion reactions.

3. The value of the biologic test in preventing dangerous transfusion reactions is reiterated.

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THORACOPAGUS TWINS—X-RAY DIAGNOSIS

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A CASE of thoracopagus twins is reported in which an antepartum diagnosis was not made. Several important features will be emphasized which, in the future, should make it possible to diagnose this condition roentgenologically during the antepartum period.

Case Report

The patient, a 26-year-old white primipara, had her last menstrual period January 2, 1942. The history, physical examination and laboratory findings were entirely negative. Her pelvis was ample. The antepartum course was normal. At about 28 weeks, the diagnosis of twins was made on physical examination. At 36 weeks, an x-ray examination definitely confirmed this diagnosis and also verified the position of the babies (Fig. 1).

Inasmuch as it was thought desirable to prolong the intrauterine life of the babies as long as possible, the patient was given 10 mg. progesterone twice weekly from the thirtieth week until delivery. She was also given 10 mg. ephynal acetate three times daily. During this period the patient had two-plus ankle edema, but no other complaints or abnormal findings.

On October 2, 1942, at 6 A.M. the patient was admitted to the hospital. The membranes had ruptured two hours earlier. The diagnosis of twins, double breech was made. Neither buttock was engaged. The cervix was dilated 2 fingerbreadths, and thin. Two fetal hearts were definitely heard, one to the right and the other to the left above the level of the umbilicus.

At 10 A.M. the cervix was dilated 2½ fingerbreadths, and pains were strong every 5 minutes. The patient was given nembutal (gr. iii) by mouth, scopolamine (gr. $\frac{1}{200}$) subcutaneously and vitamin K (mg. 3.3) subcutaneously.

At 1 P.M. the patient had 3-minute pains. A sterile vaginal examination showed the cervix fully dilated and a double footling breech at the level of the spines. The patient was awake and rational, and was requested to bear down with her pains.

Three hours later, there was very slight descent, but no important progress. The patient was exhausted from her efforts and both fetal hearts had slowed considerably, the rate dropping from 150 to 100 beats per minute.

In view of the lack of progress and fetal distress, active intervention was decided upon. The patient was prepared and catheterized and local infiltration of the perineum with ½ per cent procaine was completed. The baby on the right seemed to be presenting. The anterior foot was grasped and pulled out of the vagina and with it came two other feet spontaneously. The extra extremity was pushed out of the pelvis. On gentle traction of the extremities, the right baby descended so that its pelvis was just above the introitus, but it could not be extracted further. The traction forced the two lower extremities of the baby on the left to

prolapse through the vaginal opening and they could not be forced back out of the pelvis. Finally, all four legs were pulled into the vagina. The patient was given a general anesthesia and exploration of the upper vagina and uterus was attempted. This revealed a union of the babies at the umbilicus and in the region of the chest.

Fig. 1.

Several unsuccessful attempts were made to deliver these babies in the manner advocated by Williams, i.e., forcing one up and the other down and then also trying to bring both down together, forcing the head of one into the concavity of the neck of the other. The union between the babies seemed very solid and there was very little mobility.

Finally, the fetal heart sounds were lost and it was noticed that the one cord which went to both babies had ceased pulsating. A destructive operation was then decided upon after consultation with Dr. M. Goldberger.

A Jacobson hook was introduced into the uterus between the babies and pulled downward, separating them. The uterus was extremely ir-

ritable by this time and a Bandl's ring had formed which held both children firmly. After rather difficult pulling and further destruction of the babies, the right twin was delivered, and then finally the left. Both infants were eviscerated and dead. The placenta, about 8 inches in diameter, had one cord which had 6 vessels in it. It went completely as one to the babies, and apparently divided just before each group of vessels entered the umbilicus of the respective baby.

The entire procedure had taken almost an hour, but the mother's condition seemed fair after the delivery of the children. There was about 500 c.c. blood loss after the delivery of the placenta. It was deemed advisable to return the mother to her room without attempting to repair the episiotomy. She was given an intravenous infusion of 1,000 c.c., 5 per cent glucose in saline.

The mother's postpartum course was uneventful. On the fifth postpartum day, she was taken to the operating room and a secondary closure of the episiotomy was completed. Following débridement, the perineum was closed in layers, sulfanilamide powder being used in each layer. Her course was febrile for two days after the closure, but then the temperature returned to normal. The episiotomy healed by first intention. Examination on the fourteenth postpartum day was essentially negative, and the patient was discharged from the hospital.

An autopsy on the babies by Dr. Milton Halpern revealed these salient facts: The babies were twin girls, about 17 inches long, one weighing 5 pounds 2 ounces, and the other 5 pounds 4 ounces.

Because of the extensive damage to the babies at delivery, the entire picture was not clear. The babies each had an umbilicus, but there was only one sternum.

The heart of infant *A* was torn open and the pulmonary arteries branched off a single aorta of large caliber. There were two ventricles which communicated with each other, both opening into a common aorta. The abdominal contents were normal. The umbilical veins both united 1½ inches below the notch of the liver.

The heart of baby *B* was also ruptured. This suggested the possibility that the hearts may have been joined. This heart resembled that of baby *A*. The abdominal viscera were also the same as baby *A*. No sternum was present.

Because of the mutilation, a more detailed report could not be given.

Comment

The first question to be discussed is whether the diagnosis of thoracopagus twins could have been made before delivery. The response might have been in the affirmative if the possibility of thoracopagus had been considered when the x-ray films were studied. There are several important features which were overlooked in studying the x-ray films. In almost all twins, even bi-breech, the heads are at different levels, one being higher than the other. They are not usually at almost the same level as seen here. Furthermore, the head of the right twin does not face the front of its body, but turns to the side toward the ventral aspect of the mother, and is extended. This indicates that the babies are so close together they cannot face each other. Finally, one gets the impression that the hand of the left baby is over the shoulder of the right and the arm of the right baby goes around the left, probably indicating that the babies are in the same amniotic sac (unless there is superimposition). Furthermore, the heads are in direct apposition.

Second, was cesarean section indicated if the diagnosis had been made ante partum? Also, was it indicated when the diagnosis of thoracopagus was made in this case? Many diverse opinions will be expressed in answering these questions. It has long been an obstetric rule that if one anomaly exists, there are usually others. In view of the cardiac pathology found on autopsy, these babies could not have survived. Therefore, I do not believe that cesarean section is warranted even if the diagnosis is made. If the union is merely that of skin attachment, there will be sufficient elasticity to allow the babies to deliver spontaneously. If the attachment is deeper, other anomalies are probably present. Certainly, in this particular case, the danger to the mother did not justify cesarean section.

Finally, it should be pointed out that in prolonged operative deliveries, delayed closure of the perineum is not the dangerous and unsuccessful procedure it was before the advent of sulfonamide drugs. This patient had no preoperative preparation of the wound. It was covered with a grayish membrane and had the characteristic fetid odor of saprophytic infection. Yet by simple débridement and the use of sulfanilamide in the closure, healing was prompt and complete. The expediency of delayed closure of episiotomy in cases of this type must be emphasized.

521 Park Avenue

UNUSUAL SEQUEL TO ATTEMPTED CRIMINAL ABORTION

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(From the Woman's Hospital)

INSTANCES of perforation of the uterus by criminal abortionists are so common, that they ordinarily occasion only passing comment. I feel, however, that the following case presents several features that are sufficiently unique to warrant its being placed on record.

The patient was Miss A. V., aged 33, a short, stocky woman of Slavish extraction, who weighed 63.5 kilograms (140 pounds), and was quite obviously equipped with a heritage of unusual bodily strength and stamina. She was first seen at the Woman's Hospital of Pittsburgh on October 10, 1943. She had walked to the hospital and seemed fairly comfortable. She was complaining of abdominal pain, chiefly in the right upper and lower quadrant, and to a lesser extent, in the left upper quadrant. For a week previously, she had had pain in both lower quadrants. The pain was sharp in character, definitely not crampy, fairly severe at all times, but excruciating during and immediately following defecation. There had been no nausea or vomiting, in fact no other symptoms whatever.

Eight days before admission, she had visited a criminal abortionist, being, as she thought, 3½ months pregnant. She was uncertain as to the date of her last menstrual period, but thought that it was about the last of June. The abortionist placed a long rubber tube in the grasp probably of a uterine dressing forceps and introduced it, as he told her, "into the womb." She felt a stab of intense pain as this was done. Gauze was packed into the vagina, and she was instructed to remove this the next day. She did this, and the end of the tube immediately protruded from the vulva. She pushed this back into the vagina and wore an ordinary sanitary pad and belt to keep it there.

She stated that the vaginal gauze removed was bloodstained and that a few drops of blood were passed during the next few hours, but none subsequently. Lower abdominal pain had begun and was fairly severe, but it was not crampy in character and there was no discharge of amniotic fluid.

During the ensuing six days, the end of the tube slipped out of the vagina several times, and was each time digitally replaced. On the seventh day, when the end of the tube came out again, she followed it up the vagina with her finger and found it extending into the cervix. In some manner, guided by the finger in the vagina, she succeeded in pushing the entire tube through the cervix. It did not come out again and she thought the pain was a little worse for a short time.

Throughout the entire seven days, she had worked every day at her usual occupation. She came to the hospital on the eighth day because her pain seemed a little worse, and because she had become alarmed by the failure of the tube and fetus to be expelled as she had been promised.

She was immediately admitted to the hospital. Her temperature was 98.8° F., pulse 82, and respiration 18. She seemed only slightly un-

comfortable. The leucocyte count was 14,600, red cells 3,740,000, and hemoglobin 77 per cent. Sedimentation rate was 18 mm. in 52 minutes. There were no abnormal findings in the catheterized urine. On physical examination, there was slight generalized abdominal tenderness, no more marked in one area than another. There was no distention, and peristalsis was normal. The fundus of the uterus was palpable, three fingerbreadths above the symphysis pubis. Fetal heart sounds were not audible. Vaginal examination revealed only the usual signs of normal pregnancy. The cervix was soft and closed. No foreign body was palpable. There was no blood, and no abnormal vaginal discharge.

Fig. 1.—Roentgenogram showing catheter in situ.

The accompanying x-ray was taken and showed a long thick rubber tube lying across the abdomen, free in the cavity. One end was sharply curved and extended upward along the cecum and reached a point apparently behind the liver. The remainder extended across the abdomen at the level of the iliac crests and roughly paralleled the course of the duodenum. (Fig. 1.)

Laparotomy was done the next day. Through a low right pararectus incision, the tube was easily found and removed. The abdominal cavity contained a moderate amount of thin and odorless, but definitely purulent fluid. A smear from this showed gram-positive cocci singly and in short chains. Culture reported four days later showed the presence of *Streptococcus viridans* and *Staphylococcus aureus.* The site of the uterine perforation was found in the midline of the uterus posteriorly just above the level of the internal os, and firmly sealed by dense adhesion of a portion of the sigmoid flexure. About this adhesion, there

was a heavy fibrinous exudate. The entire peritoneum showed the signs of active inflammation, though with very little fibrinous exudate. There were no other adhesions. The sigmoid-uterine adhesion was not disturbed. Four grams of sulfanilamide were placed in the abdominal cavity, and the peritoneum closed without drainage. An additional gram of sulfanilamide was placed in the wound and the remainder of the closure was routine. The tube removed was a small-caliber rectal tube measuring 40 cm. in length by 9 mm. in diameter.

The day after operation, the patient's highest temperature was 100° F. On the second postoperative day, the highest temperature recorded was 99.2° F., and the pulse 82. From the third day on, both pulse and temperature were normal. No sulfadrugs were given after the operation. She had no vomiting or distention, and never required catheterization. She had an enema on the fourth postoperative day, and thereafter, action of the bowels was normal. She was restored to a full diet on the fifth day after operation, allowed out of bed on the eleventh day, and discharged on the fourteenth, free from all symptoms.

The pregnancy proceeded normally until April 1, 1944. At this time, the patient suddenly developed generalized edema, hypertension, and albuminuria. She was placed on a regimen consisting of bed rest, high protein diet, sedation, restriction of fluid intake, and moderate doses of magnesium sulfate every other day. She was admitted to the Elizabeth Steele Magee Hospital on April 11, 1944. Blood pressure on admission was not unduly high, 156/92, and there was only a trace of albumin in the urine. The edema, however, was more marked than it had been, and she was complaining of headache, dizziness, and slight visual disturbances. It was feared that a disaster was impending. For this reason and because of uncertainty as to the behavior of the sigmoid-uterine adhesion during labor, a low cervical cesarean section was performed April 12. The baby was a healthy, normally developed boy weighing 3,295 grams (7 pounds, 4 ounces). From within the uterus, the site of the previous perforation could not be identified. After closure of the uterus, the sigmoid adhesion noted at the previous operation was still found to be present. There were no other adhesions, and the peritoneum appeared normal.

Recovery from this operation was uneventful. The wound healed by first intention. The edema disappeared within a week, as did all other pre-eclamptic symptoms. She was discharged on the fifteenth postoperative day symptom-free and with a blood pressure of 140/80. She was not seen again until May 26, at which time postpartum examination revealed entirely normal findings, and the blood pressure was 120/68. On June 9, the blood pressure was 122/70, and she was finally discharged, free from all complaints. The infant is developing normally.

The striking features of this case are the degree of abuse which the uterus withstood without aborting, and the tremendous resistance of the patient to infection. The pre-eclamptic toxemia might well have developed had nothing else happened.

JENKINS ARCADE

TORSION OF APPARENTLY NORMAL OVARY, AND SPONTANEOUS AMPUTATION OF FALLOPIAN TUBE DURING ADOLESCENCE

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TORSION of the normal uterine adnexal organs during childhood, especially if accompanied by spontaneous amputation of the Fallopian tube, is a rare operative finding. Neel and Virnig[1] state that the reason for relative infrequency of ovarian tumors in childhood very likely serves as an explanation for the rarity with which twisted ovarian tumors or cysts are encountered during childhood. They cite Smith and Butler,[2] who state that only 25 instances of torsion of ovarian tumors before puberty were reported in the literature up until 1921. They also state that only 14 cases of torsion of the normal adnexa could be found, and of these, only 4 were under twelve years of age. Schute,[3] in 1932, stated that 35 cases of torsion of the normal ovary had been reported. In the ensuing nine years, several cases have been described, mostly in the foreign literature, but from figures available, it is obvious that torsion of the normal uterine adnexa is not common. We have been unable to find any authentic report upon spontaneous amputation of the normal Fallopian tube during childhood. Barrett and Lash[4] report a case of spontaneous amputation of the tube in a patient 40 years of age, and also cite Ries, who in 1900, described the bilateral amputation of the tubes in an adult, 32 years of age.

Case Report

The major complaint was pain in the left lower quadrant accompanied by vomiting. This patient, aged 12 years, had always been well and healthy until the day before her hospital admittance, at which time she developed a severe pain in the left lower quadrant. This continued throughout the day, and in the evening the patient vomited and remained nauseated and continued to vomit all evening. She was seen by Dr. A. G. Dow, who thought possibly she had some difficulty with the left ovary and prescribed for her. She continued to have pain and to vomit throughout the night of August 31, and was seen by the author late in the afternoon of September 1. At that time, the pain was located in both lower quadrants, although more on the left than on the right. She was also quite distended and showed considerable rectus rigidity and rebound tenderness. Nothing relieved the patient's condition and a diagnosis of an acute abdomen was made. This patient had menstruated quite regularly for one year and was due to have a regular menstrual period on September 2, 1943. Upon physical examination, she appeared anxious and had the facial appearance resembling one with peritonitis and complained of pain over the entire lower quadrant, particularly on the left. The diagnosis lay between ovary on a twisted pedicle or rupture of some hollow viscus, possibly appendiceal. Her temperature upon hospital admittance was 100.4° F.; pulse 114; respiration 30. Lab-

oratory reports: hemoglobin 81 per cent; R.B.C. 4,940,000; W.B.C. 23,100; 84 polymorphonuclear; 12 staff; 4 young; 4 baso; 6 lymph; 6 mono. Urinalysis showed a trace of albumin, 3 per cent acetone.

Recognizing the acute condition present the patient was taken to the operating room and a midline incision was made. A retort-shaped mass was found in the cul-de-sac of Douglas, dark purple in color, the distal end about the size of a small grapefruit, pushing the uterus forward and filling the entire cul-de-sac, and because of its size and location in the hollow of the sacrum, it was difficult to deliver it out of the cul-de-sac into the abdomen. At the left cornu of the uterus, the tube was found missing and the only evidence of it was found in a stump about 1.5 centimeters in length which was well sealed off and showed no evidence of bleeding. Right tube and ovary were normal. Appendix was found to be retrocecal. The stump of the left tube was removed and the retort-shaped mass was found to be the remaining portion of the left tube containing a hematosalpinx, the fimbriated end of which had been sealed off by some process. The abdomen was closed in layers.

This patient was supported by fluids and made an uneventful recovery, and was dismissed from the hospital on the tenth postoperative day.

Pathological Report (H. E. Eggers, M.D.).—Sections of the greatly distended tube showed this to be filled with hemorrhagic material. This occurred not only in the lumen, but in the wall as well, with resultant marked distorsion. Around the vessels of the wall, there was almost uniform cuffing with infiltrated leucocytes.

Diagnosis: Hemosalpinx.

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Special Article

REPORT ON AN ENGLISH NATIONAL MATERNITY SERVICE

A Digest With Comment*

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AT THE request of the Royal College of Obstetricians and Gynecologists, a committee of English obstetricians under the chairmanship of Dr. Eardley Holland has surveyed the present practice of obstetrics in England and Wales and made certain proposals for an improved maternity program on a broad national basis. The findings and recommendations of the committee make up a forty-two page pamphlet recently issued under the title, *"Report on a National Maternity Service."*

As may be seen from the following list, the committee members are men and women of eminence, several of whom have visited this country as honorary guests of one or another of our national societies: Eardley Holland, M.D. (Chairman), Dugald Baird, M.D., A. C. H. Bell, M.B., J. B. Blaikley, M.B., Alice Bloomfield, M.D., Francis J. Browne, M.D., Daniel Dougal, M.D., E. C. Fahmy, M.B., A. A. Gemmell, M.D., Surg.-Comdr. E. A. Gerrard, M.D., W. Gilliatt, M.S., J. P. Hedley, M. Chir., James Hendry, M.D., C. H. G. Macafee, M.B., Alan Monerieff, M.D., and James Young, M.D.

The Present Service and Its Shortcomings

Although maternal mortality rates in England and Wales have shown a gratifying diminution in recent years (from 4.49 per 1,000 live births in 1931-35 to 2.54 in 1942), the Committee believes they are still too high. It attributes the fall not so much to any improvement in the average standard of obstetric practice as to the application of new methods and drugs in the treatment of shock, hemorrhage and sepsis, and to modern technique in the investigation and prevention of bacterial infection. Thus, it points to the more prevalent use of blood and plasma transfusion, the employment of sulphonamides, the prevention of "droplet infection" by the use of face masks, the control of infection by modern barrier nursing, and the lowering of infection in hospitals by bacteriologically controlled administration and discipline. Statistics reveal that deaths from sepsis began to fall significantly in 1937, corresponding with improvements in the application of bacteriology to obstetrics and the advent of the new drugs, and deaths from other causes rather later, coinciding with the greater availability of transfusion fluids. The Committee believes also that the diminution in maternal mortality has been helped by the increase in hospitalization of maternity cases and by the better planning of their maternity services by a number of local authorities.

But the experience of the committee members as obstetrical consultants as well as two other types of evidence has convinced them that

*Prepared at the request of the Editor of the Journal.

the average standard of obstetric practice has not improved and leaves much to be desired. It is pointed out, in the first place, that the percentage of avoidable deaths remains shockingly high, ranging from 46 to 75 per cent in various reports. Secondly, the Committee notes with concern the great difference between maternal mortality rates in various parts of England. Thus, whereas this figure in 1939-1942 was 0.7 and 1.0 in Gloucester and Walsall, it was 4.2 in Oldham and Southend-on-Sea; and the opinion is expressed that this variation in maternal mortality is primarily a matter of obstetric personnel, of the individual skill of midwives, general practitioners and consultants, together with the availability of first-rate maternity institutions and equipment.

It is likewise the consensus of the report that the frequency of stillbirths, neonatal deaths and premature births is higher than it should be. Stillbirth is a problem intimately associated with the adequacy of antenatal supervision and the care given during childbirth and the puerperium. Causes of neonatal death are mainly obstetrical, premature birth being the commonest, followed closely by birth injury and infection. Prevention of these deaths is a problem for obstetrician and pediatrician in collaboration. Moreover, maternity institutions must provide modern accommodation for the newborn. In this connection the following statement is quoted: "I have been impressed by the poverty of much of the accommodation provided for the newborn baby, even in modern hospitals. There is rarely any effort to provide proper spacing of the cots. Nurses are by no means always masked, and though breast-feeding is far from universal, milk kitchens are rare. In some hospitals there is inadequate supervision of visitors to the nursery." (L. Parsons.)

But these mortality rates, although serious, are only two of the things, in the opinion of the Committee, which expose the shortcomings of the present maternity and health services. The present system has grown up in a very haphazard way so that facilities, both medical and nursing, are unevenly distributed. The deficiencies cause inconvenience, discomfort and hardship to many women at a time when things should be made easy for them. The lack of suitable maternity accommodations often makes the cost of childbirth too high, especially for parents in the middle income groups. These and other deterrents to having children lower the birth-rate.

The situation is summed up by saying that the present services are not of the class deserved by a great nation with centuries of accomplishment behind it and a great future before it. Let us give the best possible care, the report continues, to our chief national asset, the babies, and to the mothers who produce them.

Social and Economic Considerations

Although it is stressed that the primary essential for reduction of maternal mortality is sound obstetrics before, during and after birth, the Committee is not satisfied that economic and social factors can be entirely excluded. There is evidence that the mother of many children, whose income does not keep pace with the growing family, is likely to suffer from malnutrition and exhaustion. Moreover, as the social and economic order is descended from the higher ranks of business and professional men to unskilled laborers, the maternal mortality rates *in any given age group* show a definite rise.

In so far as stillbirth and neonatal mortality is concerned, the evidence is clear that adverse social and economic conditions materially reduce the chances of a child being born alive and materially increase the chances of its dying within one month of life. In Aberdeen, for instance, it was found that the women of a higher social class had a stillbirth rate of 11 per 1,000 total births, whereas those in the lower class had a rate of 30. "It seems probable that the primary difference lies in the health of the mothers. And health in this sense implies better feeding and more rest during the pregnancy, in addition to the better physique which results from good feeding and environment from birth." (*Report on Infant Mortality in Scotland,* 1943.)

The importance of a high standard of family life is urged in the belief that the infusing of higher moral and spiritual values into the families of a country has a profound bearing on physical and mental health. The Committee pleads in particular for the encouragement of early marriage. It believes, indeed, that measures for the extension of social security, with this end in mind, would have a sound biological foundation. Apart from the advantage of early marriage in relation to sexual morality and apart from its possible bearing on population problems, early marriage has a direct bearing on the health of mother and child. The risks associated with childbirth at a later age can always be minimized by skillful care and need never be a deterrent to marriage at any age, but nevertheless, over large groups, they do attain statistical significance. Education in sex and parenthood should be treated seriously, started young and given to both boys and girls. In connection with the employment of pregnant women, it is urged that expectant mothers be assured of protection from undue stress, physical and mental, during the last three months of pregnancy and the first six months after parturition.

The Type of Service Proposed

It is proposed that the country be divided into areas with a population of about 1,000,000 each yielding some 15,000 births a year. The maternity and infant needs of such an area would be sufficiently great to make full use of a complete service but not too large for obstetric consultants, resident within the area, to deal personally and promptly with the consultative, emergency and operative work. Naturally, the size would have to be governed by such factors as geography, density of population, size of towns, and transport. In the past, the distant or "telephone" consultant has been most unsatisfactory.

Each of these areas would have a central and supervising maternity center, ultimately responsible for the maternity and infant care of the whole region, known as a *Key or Primary Center.* Working in close association with this Key Center and under its general surveillance a number of *Divisional or Secondary Centers* would function, and under each of these certain *Local or Peripheral Centers.*

The Key or Primary Maternity Center.—This would be of such size, status and repute that it would be the consultative, teaching and research center of the area as well as the source of inspiration and leadership for all the other workers in the Service. Such a center would consist of a maternity unit of 100 or more lying-in beds with an appropriate number of antenatal and isolation beds, a department for infants, ambulance and emergency services, antenatal and postnatal

clinics, laboratories, classrooms and library. There would be an associated gynecological unit with provision for the treatment of abortions.

Such a Key Center would, whenever possible, be associated with a university and attached to a medical school, the Professor of Obstetrics and Gynecology being the Director of the teaching unit. He should be provided with a house in the hospital precincts. With him would be associated a staff of specialists, assistants of various grades, house surgeons, midwives and nurses. The infants would be in charge of a pediatrician who would be responsible for the general care and supervision of all infants. The Key Center would be the chief consultative center in the region for all types of cases, especially for unusual complications and would deal also with the ordinary institutional obstetrics of its district. There would be clinical laboratories of pathology and bacteriology. It would have a modern and well-staffed records department, and might be made the clearing-house for the records of the whole region.

The Divisional or Secondary Centers would be in large towns or in small towns in rural areas. They would not necessarily be smaller than the Key Centers, would be equipped just as well, would have a specialist staff, the senior of whom would live in the hospital and provide full range of service. Their beds would provide accommodation for their own booked cases as well as for complicated and emergency cases sent in from outside; they would provide, moreover, consultant services, both obstetric and pediatric for general practitioners.

In reading the report, one gathers the impression that these Divisional or Secondary Centers would function more or less independently of the Key Center in the management of individual cases, but would be subservient to it in respect to general policies, appointments and the like. One infers, moreover, that these Divisional Centers would be responsible to the Key Center for a high standard of practice.

The Local or Peripheral Centers would be small units in country towns and villages. They would be in charge of selected general practitioners in the district and would have a resident staff of nurse-midwives. They would have their own antenatal clinics, and would provide beds for women who wish to have institutional confinements, and for emergency cases for whom a more distant journey would be dangerous. They would be in close touch with the nearest Divisional Center, from which the specialist staff would come for consultations or operations. They would be centers for the district midwives and health visitors (presumably public health nurses), whose residential quarters might be attached. These would be the outposts of the Service, always linked with the Divisional Centers and through them with the Key Center.

Institutional Obstetrics.—Modern institutional obstetrics, the report goes on, can be made remarkably safe, and convincing statistics are cited in support of this statement. During the war the Ministry of Health has brought about an increase of 3,000 maternity beds in England and Wales so that there is now maternity accommodation in institutions for at least 50 per cent of the mothers of the country. But the Committee is firm in its belief that this is not enough and that there is a shortage and bad distribution of maternity beds for all classes of the community. It recommends providing, to begin with, for about 70 per cent of all births. The number required for a region with 15,000 births a year may be reckoned by allowing 20 patients a

year for each lying-in bed, with a proportion of antenatal beds equal to one-third of the lying-in beds. For 70 per cent of 15,000 births, on this basis, 525 lying-in beds would be needed and 175 antenatal beds, a total of 700 maternity beds to be apportioned among the various maternity centers.

Home Obstetrics.—Delivery of women in their own homes is approved provided that three conditions are observed. One is that the women are carefully selected and have had excellent antenatal supervision up to the very end of pregnancy. Another is that all primigravidae, all women who have had six children or more, all whose labors are likely to be abnormal, and all whose home conditions are unsuitable, should be excluded. The third condition to ensure safety is that home obstetrics should be supported by obstetric consultants and maternity institutions. Expert help can then be sent when required without delay or difficulty, or the patient can be moved into an institution by ambulance.

Antenatal Care.—Antenatal care must not be regarded as an end in itself, isolated from the management of labor. Pregnancy, labor and the puerperium are all of a piece and should have continuity of supervision from the same doctor or institution. Every antenatal clinic should be linked to a Maternity Center with a sufficient number of antenatal beds. The number of such antenatal beds should not be less than one-third of the lying-in beds. These are required for simple rest and observation, as well as for the treatment of complications. To take an elderly multipara, with children of all ages to look after, into a rest-bed for the last two or three weeks of pregnancy may be life-saving. A common fault in antenatal clinics is that there are too many patients per session. The consequence is that the work consists chiefly in a hunt for abnormalities and far too little time and attention are being given to the personal and educational sides (general health, rest, diet, sleep, comfort). There should be an appointment system for the patients to prevent long waits and waste of time.

Postnatal and Infant Health Clinics.—It is believed that the custom of mothers and babies attending clinics together, in the postnatal period, has much to recommend it since here the obstetrician and pediatrician can meet on common ground. However, a most critical time for the infant, as well as the mother, is the period between discharge from the hospital and the first visit to the postnatal and infant health clinic. Better continuity of supervision must be established here. Ideally the health visitor (public health nurse) should know by personal interview at the hospital or by prompt dispatch of a document, all details of the infant's feedings and should call at the mother's home on the day after the mother leaves the hospital.

Postnatal Hostels.—Many women after childbirth would be all the better for a period of recuperation or rehabilitation beyond the usual 10 to 14 days in bed at home or in a hospital. Just as an antenatal department requires to be supported with antenatal beds for pregnant women who are ill so does a postnatal department require to be supported, but in a different manner. The few weeks following the birth of a baby are a period of adjustment, especially for a young mother with her first baby. She has new worries, anxieties and responsibilities and must arrange her life to meet them. What she needs is a short period of rest and guidance, freedom from worry and household responsibilities, all the more if she is anemic or debilitated, or

has had a difficult labor or if there is trouble with lactation and the baby does not thrive. Two or more weeks in a postnatal hostel would make all the difference to the health and happiness of mother and baby. Postnatal hostels should be linked with a Maternity Center and be administratively part of the regional maternity service.

Personnel of the Service.—The chief obstetrician of a Key Maternity Center should be a clinician, a teacher and a leader. He would have great responsibilities not only in setting the standard for the whole region, but in the selection and training of young obstetricians. When possible he would have the status of a professor attached to a university. The first problem in personnel, the report continues, would be to find enough trained obstetricians and gynecologists. In the opinion of the Committee, such specialists require a postgraduate training of at least five years, the first two to be spent in acquiring more knowledge of medicine, surgery and laboratory science, and the last three in graded resident appointments in approved obstetric and gynecologic hospitals. It is one of the objects of the Royal College of Obstetricians and Gynecologists to encourage the training of specialists and to set the requisite standard and maintain it. There are, at present, in Great Britain 167 Fellows and 285 Members.

The Committee realizes that every registered medical practitioner is entitled by law to practice all branches of medicine and that it would be an interference with that right to make obstetric practice conditional on special postgraduate study and the possession of a special diploma. But it believes that he should have had special experience in this work. The Committee believes that general practitioners should take an important share in a National Maternity Service but its belief is equally strong that it is not an advantage to childbearing women that *any* practitioner should practice obstetrics and be employed in a National Maternity Service but only those with special experience. The Royal College of Obstetricians and Gynecologists grants a diploma in obstetrics to general practitioners and at present there are 332 diplomates. *The present system often places general practitioners in impossible situations. Unaided, and in unsuitable surroundings, they may have to deal with complications that would test the skill of the most eminent specialists. General practitioners and their patients should be supported and protected by a maternity service that makes provision for such situations and provides emergency transport of specialists to patients and patients to Maternity Centers.*

A remarkable feature of British obstetrics in this century is the steady rise of the midwife to a position in which she is present at about 90 per cent of the confinements and in three-quarters of these she acts as an independent practitioner with full responsibility. In 1942 there were approximately 15,000 practicing midwives on the register, about 12,250 of whom were in home practice, the remainder being employed in maternity institutions. The training of the midwife has been progressively improved and she now has to complete a course of one year if she is a state registered nurse and of two years otherwise. Midwives are conservative practitioners, aiming at natural labors, and their results are excellent.

Good as is the work done by midwives the Committee believes it could be better. They should be trained in large Maternity Centers with a first-class obstetric staff and not in a large number of petty training schools in small hospitals. Midwives should not be regarded as competent to undertake unaided the antenatal care of the expectant

mother, but should always work in collaboration with the general practitioner or the obstetrician of the clinic. When a midwife summons medical aid she usually sends for the patient's general practitioner. Better results might be expected if midwives summoned aid only from practitioners with special obstetric experience and if their work were more closely keyed into the Maternity Centers. Every midwife should be a Registered Nurse.

It is estimated that the total number of public health nurses (health visitors) engaged in maternity and child welfare work is equivalent to a whole time service of about 2,450, a number that is quite inadequate for the proper performance of home visiting. But even more important than increase of staffs is full cooperation between hospital or midwife and public health nurse. Ideally the public health nurse should call at the home the day after the mother and infant return from the hospital to help in tiding over a difficult period in which much unnecessary weaning and dietetic experiments take place.

Administration.—The whole Service should act as a single unit, with all parts integrated—maternity centers, antenatal and other clinics, obstetricians, pediatricians, general practitioners, midwives, public health nurses, etc. The Committee regards this principle of integration as absolutely essential for efficiency and feels, therefore, that it should be under a single administrative authority. It is assumed that the Minister of Health, together with competent advisors, would control such a maternity and infant health service and that it would be a component part of the general health service of the country.

Comment

This thoughtful and forward-looking survey of maternity needs in England cannot help but cause American obstetricians to ponder corresponding problems in this country. Among these problems are:

1. *What has caused the recent decline in maternal mortality?* In the United States as well as in England the maternal mortality rate has fallen dramatically over the past decade. Here, among white women, it declined between 1931 and 1941 from 60 to 27 deaths per 10,000 live births, whereas there, the diminution over the ten-year period was from 45 to 28. The Report stresses the fact that in England this fall in maternal mortality is attributable not to better standards in obstetric practice (training, skill, judgment), but to certain technical advances, notably more blood transfusion, sulfonamides and better hospital technique. Beyond question these same factors have played a most important part in the reduction of maternal mortality in the United States, but to assign them sole credit here is scarcely just. It would seem a valid assumption that the technical advances mentioned have been equally utilized in the two countries and have yielded comparable results in respect to saving of mothers' lives. Accordingly, if the reduction in maternal mortality in one of the countries greatly exceeded that in the other, the difference in all probability would be attributable to causes over and above technical advances. Now, as shown by the above figures, the decline in the maternal death rate in the United States has been greater than that in England by about one-third; and the question arises as to whether this differential may not be due to improved standards of obstetrics in this country.

It was in the decade of the thirties, let it be recalled, that numerous maternal mortality committees throughout the United States started

analyzing maternal deaths and at meetings open to the profession began discussing, in no supine language, their preventability. It was during the same decade that the American Board of Obstetrics and Gynecology was founded. At about the same time the Children's Bureau gave great impetus to public health nursing in obstetrics, so that, by 1939, 5,329 nurses, in 1,963 counties, were working in maternal and child health services and, with the help of the Bureau, State Health Departments began developing widespread teaching and consultative programs for general practitioners engaged in maternity work. Meanwhile, two great Congresses of Obstetrics and Gynecology were held where thousands of physicians and nurses received instruction and stimulation. The fact that these many agencies were established does not necessarily mean that results were achieved, but here and there evidence is continually cropping up that the efforts of these workers have not been in vain and that a substantial part of the recent reduction in our maternal mortality has been due to better obstetrics. But it should be noted as a chastening thought that we are only now catching up with the English rate.

2. *The problem of the general practitioner.* It would be no exaggeration to say that the body of knowledge which a general practitioner should have at his disposal today is twice that necessary just a few decades ago. Thus, in obstetrics he should have gained a passing acquaintance, at least, with countless new facts and techniques, from the Rh factor to x-ray pelvimetry. The increase in knowledge in other fields has possibly been even greater. To expect the average busy practitioner to assimilate and utilize all this and hence be "almost a specialist" in all fields, is wishful thinking. Yet, in isolated homes and with inadequate equipment, he is asked to attend all alone every type of obstetric case. Nineteen times out of twenty, everything terminates happily, but now and then he is faced with a complication of such gravity that the skill of the most expert obstetrician in the best equipped maternity would be taxed. This is the type of case that ultimately comes before the local maternal mortality committee and is called "preventable." It might well have been prevented had facilities been available for immediate consultation with an obstetric specialist and immediate transfer of the patient to a modern maternity hospital. "The present system often places general practitioners in impossible situations," says the Report, a statement even more true in this country than in England because a larger percentage of American women are attended by general practitioners.

The general practitioner must be supported—not in any haphazard manner as at present, not through consultation with another general practitioner—but by a pre-arranged plan which provides for immediate consultation, when necessary, with a specialist and speedy transport of the patient to a maternity hospital. State and county medical societies, as well as State and County public officials, should look into the possibility of working out such a plan.

3. *The problem of the midwife.* In the eastern section of Maryland (which is separated from the Baltimore and Washington districts by the Chesapeake Bay and is hence more or less isolated) there live a large number of Negro families, for the most part in rural areas. Expectant mothers in this group attend regularly a prenatal clinic conducted by the County Health Department and located in the county seat. There they are seen by a local practicing physician (with special obstetric training), a graduate nurse-midwife and several negro mid-

wives. The Negro midwives have had a year's training or more under the graduate nurse-midwife and at the prenatal clinic. Cases are carefully screened, primigravidae and women with any abnormality being scheduled for hospital delivery. The normal multiparae, who constitute the bulk of the clientele, call one of the negro midwives when pains begin and labor is attended by her throughout, provided no suggestion of an abnormality develops. In the latter contingency the graduate nurse-midwife is called, who in turn, after investigating the situation, reports conditions to the physician mentioned above. According to the nature of the complication, the physician may handle the case in the local hospital or refer it to one of the university hospitals in Baltimore. The Negro midwives are in private practice, so to speak, but handle only those cases which have been approved by the County Health Department, under whose surveillance they work. They receive, from the patient, $15.00 for each confinement.

This program, worked out on a small scale to meet a local need, has functioned most satisfactorily. The patient is protected at all stages and her attendants are always supported, and through pre-arranged plan, by those with greater experience and more complete facilities.

In England, according to the Report, the majority of confinements are attended solely by midwives and with excellent results. The situation in the United States is not comparable since a rather general disapproval of midwives in this country has reduced them almost to the vanishing point. It looks now as if the pendulum may have swung too far, because it is becoming increasingly clear that well-trained and carefully supervised midwives have an important place in maternity programs for certain areas and among certain population groups where medical care is limited.

The maternal mortality rate for Negresses in the United States in 1941 was 69 per 10,000 live births or more than twice the figure for white women. About one-half of these colored mothers have no medical attendance whatsoever in pregnancy and labor. A carefully supervised midwife program would seem the best solution for this problem.

The Need for Maternity Beds.—The scandalous shortage of obstetric beds in many of our larger cities is brought poignantly to our attention by the Report's recommendation that the average hospital stay be eighteen days (twenty deliveries per bed per year). A ten-day stay is considered a luxury today in many American localities. The ratio of obstetric beds to population, as advised in the Report, seems about right and may well be noted by those responsible for maternity programs. Equally important is distribution, particularly in the more sparsely populated districts of the country. No woman in labor should be more than fifty miles from a well-equipped obstetric hospital unit with a specialist in attendance.

In sum, the Report stresses the need for a well-integrated *system* of maternity care. In this country also there is reason for believing that better organization of our resources in this field would yield significant results in terms of lowered maternal and fetal mortality rates.

THE LYING-IN HOSPITAL OF NEW YORK

IT WILL be difficult to give in detail within these few pages the history of an institution which covers the past 145 years. This was admirably recorded in 1938 by Dr. James A. Harrar, former chief surgeon, in his presentation of "The Story of The Lying-In Hospital." I have borrowed freely from this in presenting the history of the institution.

In 1798, through the efforts of 224 subscribers, the financial foundation for The Lying-In Hospital was established. "The very comfortable asylum for women whose circumstances will not enable them to make provision for their confinement in childbed" was opened in August, 1799. Its existence was brief for its doors were closed during the second year. In 1801, however, the use of the "square ward" of the New York Hospital was granted to The Lying-In Hospital. In that same year male medical students were permitted in the maternity ward to witness deliveries. This was the first time that such a privilege had been granted to male students in this country. Except for a brief period between June 9, 1822, and May 7, 1823, this union with The New York Hospital continued until June 10, 1827, when the Lying-In ward was permanently closed.

The Society of The Lying-In Hospital remained inactive until August, 1892, when it absorbed the Midwifery Dispensary which had been organized in 1888. The Midwifery Dispensary had been established through the efforts of Drs. James W. Markoe, Samuel Lambert, H. McM. Painter, and J. Clifton Edgar for the training of medical students in home deliveries. The 199 confinements during the first year increased to 2,583 during the third year, when it became a part of *The Society of The Lying-In Hospital.* In 1894 a suitable building to house The Lying-In Hospital was obtained in addition to the dispensary. This was the former residence of Hamilton Fish, located at Second Avenue and 17th Street. It provided accommodations for 32 patients and the necessary operating and delivery rooms and facilities for the staff of doctors and nurses. In 1902 the hospital was moved to the new eight-story building, which had been built for its use on the same site.

Until 1932 these facilities made possible the teaching of thousands of undergraduate and graduate physicians. The teaching in the medical schools at that time was limited to didactic and clinical lectures. The large outdoor service, therefore, provided the only means whereby the students, under the supervision of the house staff and attending surgeons, came in actual contact with patients. They not only performed the deliveries and witnessed and assisted at operations, but also gave anesthetics and the necessary postpartum care. In some years as many as 3,000 cases were handled on the outdoor service, thus providing a satisfactory insight into obstetric practice to many prospective young physicians. The district covered by the service extended from the Battery to 42nd Street, the antenatal care being rendered in two clinics; one at the main hospital and the other on Broome Street on the lower east side. Abnormal cases were transferred by ambulance from the home to the hospital. The good results obtained were evidenced as

early as 1918 when the hospital was able to report the maternal mortalities in their first 69,071 consecutive tenement house confinements as 218, one in every 317 labors, or 3.156 per thousand births. These statistics

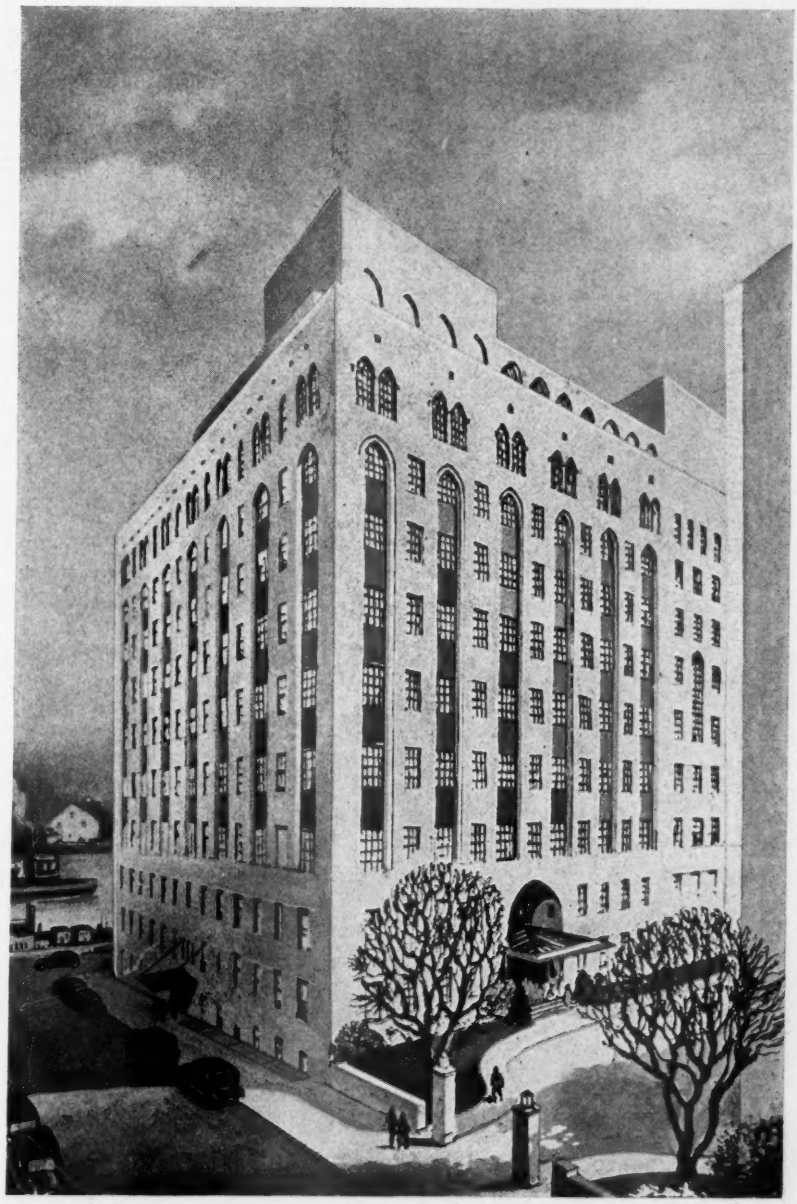

Fig. 1.—The new Lying-In Hospital—September, 1932.

are uncorrected and include all cases transferred during labor or postpartum into the Lying-In or other hospitals and dying there.

The teaching of students and physicians was not limited to the outdoor service. An average of 43 house officers, 101 undergraduate stu-

dents, and 51 postgraduate students were graduated every year. In the thirty-year period between 1902 and 1932, over 5,800 doctors were given a brief bedside instruction and experience in actual deliveries. The 200,270 babies delivered since 1890, indoor and outdoor service combined, offered ample opportunities for the training of these men.

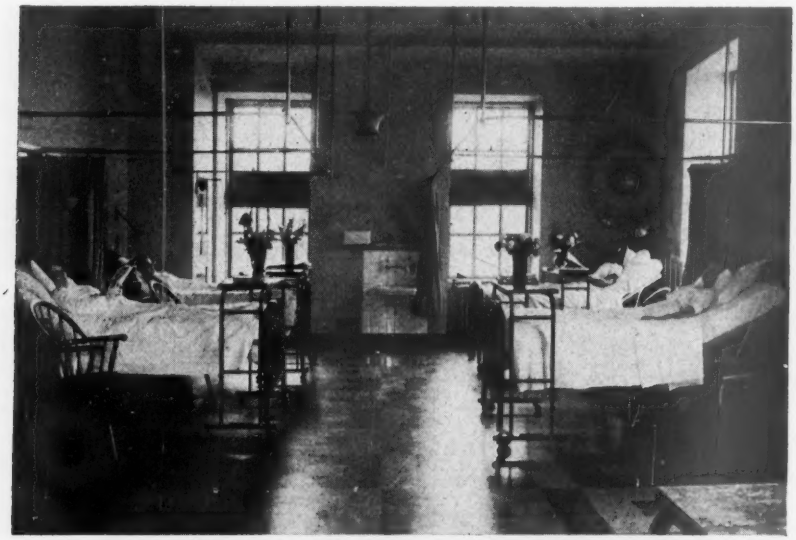

Fig. 2.—Photograph showing a typical four-bed ward.

Fig. 3.—Photograph of a typical delivery room.

The Lying-In Hospital likewise contributed greatly to the field of research. It established one of the first obstetric pathology laboratories in the country. The hospital pioneered in research on relief of pain during labor which culminated in the use of morphine and scopolamine

hypodermically, followed by the rectal instillation of ether in oil. This method was based on the original work of Dr. James Gwathmey, the anesthetist at the hospital.

In 1904 the *Bulletin of the Lying-In Hospital* made its first appearance as a scientific publication. The Bulletin appeared at intervals until 1932 when it was discontinued.

The Lying-In Hospital remained a separate institution until 1928 when it again became a part of The New York Hospital after a lapse of 101 years. This was made possible through the generosity of four individuals who subscribed the $6,000,000 necessary for the merger. At that time The New York Hospital, with Cornell University Medical College, was contemplating new buildings for their joint enterprise.

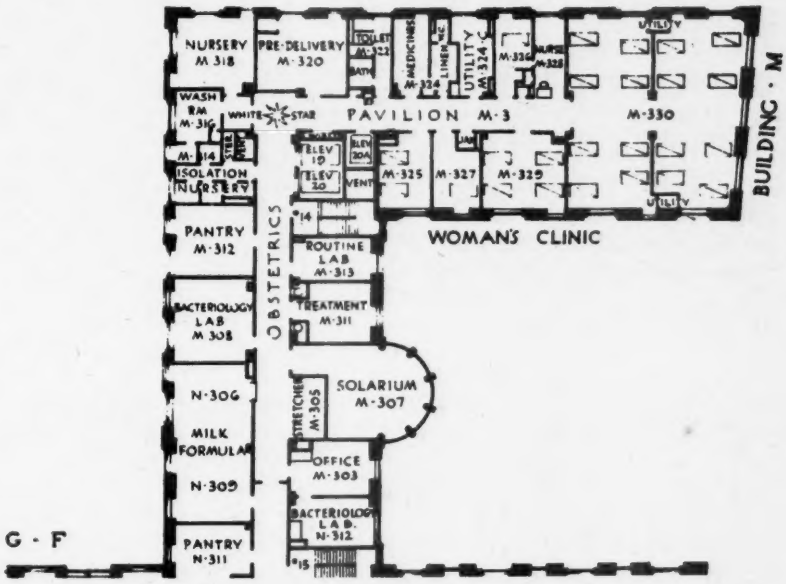

Fig. 4.—Floor plan of a typical obstetrical ward.

The present Lying-In Hospital or the *Woman's Clinic of The New York Hospital* is part of the 1,000-bed medical center located between 68th and 71st Streets from York Avenue to the East River. The eleven-story building housing The Lying-In Hospital has complete facilities for teaching and research in addition to outpatient service and accommodations for 192 patients. With the new affiliation The Lying-In became a combined Obstetrical and Gynecological Clinic. Of the total number of beds, 26 rooms are available for private patients and 36 beds for semiprivate patients. Of the 130 ward beds, 40 are devoted exclusively to gynecology. Isolation cases are cared for on one floor devoted entirely to this purpose. In itself and as part of the medical center it presents every opportunity for the teaching of medical students and house staff and for investigative work in all the branches of its specialities.

The medical staff, under the direction of Dr. H. J. Stander, obstetrician and gynecologist in chief and professor of obstetrics and gynecology, is composed of both full- and part-time physicians. No courtesy staff

is maintained. Each member of the staff shares in the teaching of students and in the supervision of the care of ward patients. The full-time staff devotes all of its time to teaching, research, and the care of patients.

The prewar schedule called for a house staff of 18 members. Six interns are appointed each year for a period of two years. At the end of the second year two interns are selected to complete the residency of five years. With each succeeding year of training the house staff assumes greater responsibility so that during the final year (fifth year) the residents are directly responsible for the care of the ward patients. Throughout the period of training the schedule is arranged to permit equal distribution of work between obstetrics and gynecology, and ample opportunity is afforded for original investigative work. The house staff assists the attending staff in the care of their private and semiprivate patients. The home delivery service was discontinued in 1942. By special arrangement the Pediatric Department of The New York Hospital cares for the premature babies born in The Lying-In Hospital and is consulted whenever indicated in the care of the newborn infant in the nurseries. This offers an excellent opportunity for the house staff to study the problems associated with the care of the newborn infant.

With the exception of serology and postmortem examinations, all the necessary examinations, including bacteriology, chemistry, pathology, and x-ray are performed at The Lying-In Hospital. This arrangement permits the utilization of such facilities for investigative work of all types. House staff participation in these departments is encouraged as a basis for the sound practice of obstetrics and gynecology.

The eighth floor of the building is devoted entirely to delivery rooms, operating rooms, and labor rooms. Two operating rooms are used for gynecological operations. The senior medical students devote two months to work in obstetrics and gynecology, and during this period they are housed within the building so that they may observe and assist with major complications whenever they occur.

The lower floor is devoted to the outpatient service. In addition to the routine obstetrical and gynecological clinics, specialty clinics are conducted. These include cardiac, toxemia, postpartum, cystoscopy, sterility, endocrine, radiation, etc.

Special staff conferences are held each Monday and staff rounds each Friday. Journal Club meetings are held monthly.

Since the opening of the new building in 1932 (Sept. 1, 1932-Dec. 31, 1943), The Lying-In Hospital has cared for 46,861 obstetrical patients and 12,262 gynecological patients. The yearly averages are 3,300 deliveries and 1,100 operations. The data of all these cases are available for study on the special punch card system which has been maintained since 1932.

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Selected Abstracts

Extrauterine Pregnancy

Alvarez, Cesar Sotolongo and Boullon, Roberto Curiel: Interstitial Tubal Pregnancy, Bol. Mens. Hosp. Policia Nacion. 3: 49-60, 1944.

The authors describe two cases in which the left tube was involved and ruptured during the third month of pregnancy. An atypical hysterectomy of the fundus with removal of the tube was performed in one case, and a subtotal hysterectomy with removal of the tube in the other case. Recovery was uneventful.

The authors emphasize the following points: Blood transfusion must be performed, whenever possible, before beginning the operation, to combat shock and avoid starting the anesthesia during shock, as this constitutes a grave risk for the patient. In severe hemorrhage there is no marked transition between the state of peritoneal shock and the picture of internal continuous hemorrhage, and one should not wait too long in the hope that the gravity of the condition is due entirely to shock; instead, a transfusion should be given, stimulants administered and the patient operated upon immediately, because the condition will not improve until the bleeding artery is ligated. When it is ligated, the pulse and the arterial pressure will rise gradually, and the stimulants will be of real usefulness.

The operation for ectopic pregnancy must be strictly conservative and excision limited to the organ involved by the ovular nidation. The intervention must be rapid and simple under general anesthesia; spinal anesthesia is advisable only for cases operated upon before rupture occurs and having an arterial pressure appropriate to this type of anesthesia.

J. P. GREENHILL.

Decoppet, H. F.: The Treatment of Essential Dysmenorrhea, Schweiz. med. Wchnschr. 74: 329, 1944.

In a series of 22 cases of essential dysmenorrhea, Decoppet of Lausanne made a diagnosis of hyperthyroidism in 90 per cent. He based his diagnosis on finding a B.M.R. of more than 20 per cent in 6 cases, a B.M.R. of more than 15 per cent in 5 cases, and a B.M.R. between 10 and 15 per cent in 9 cases. He attributed the dysmenorrhea in these 20 women to the hyperthyroidism, and the modus operandi was a deleterious action of thyroxin on the ovaries, by producing congestion of the ovaries at the time of menstruation. The thyroid hormone which is antagonistic to thyroxin is diiodotyrosin. The latter lowers the basal metabolic rate.

In the 20 cases of essential dysmenorrhea, the author used diiodotyrosin and secured relief in 75 per cent of the cases. The amount and duration of the flow were not influenced by the medication.

J. P. GREENHILL.

Gynecology

Da Costa, C. C.: Lymphogranulomatous Parametritis and Pelvic Cellulitis, Obst. y ginec. latino-am. **2:** 37-43, 1944.

Lymphogranulomatosis has become a fairly common disease in Rio de Janeiro especially among the lower classes, and hence, has become an important gynecologic problem. Da Costa along with H. Duek examined 1,279 prostitutes and found a positive Frei test in 41 per cent of them. In the early stages the sulfonamides may be helpful, but in the late stages when chronic edema, extensive ulceration, anorectal stenosis, etc., are present, treatment can only be palliative.

Two interesting observations were made, namely, relaxation of the anal sphincter and granulomatous parametritis and pelvic cellulitis. The anal relaxation is associated with fissures, ulcerations, stenosis, etc., and is probably due to an inflammation of the anal nerves followed by paralysis and loss of tonicity of the sphincter. The involvement of the parametrium and the pelvic cellular tissue is due to centripetal spread of the infection.

J. P. GREENHILL.

Chamberlin, George W., and Payne, Franklin L.: Urinary Tract Changes With Benign Pelvic Tumors, Radiology **42:** 117, 1944.

The authors studied 96 patients with benign pelvic tumors with reference to excretory urography before and after removal of the tumors. Obstruction and displacement or both were present in 66 patients. The position of the tumor was more important than the size. Intraligamentous tumors produced the highest evidence of alterations in the urinary tract. All of the above changes disappeared completely following removal of the tumors.

WILLIAM BERMAN.

Fluhman, C. F.: Clinical Use of Extracts From the Ovaries, J. A. M. A. **125:** 1, 1944.

The author describes the various preparations of estrogens and corpus luteum products and mentions the indications for their use. The potencies of the preparations and the suggested dosages are also mentioned. Great stress is laid upon the abuse of these hormones. An interesting chart of the various commercial preparations of estrogenic substances is included.

WILLIAM BERMAN.

Stegeman, W.: Incarcerated Pelvic Kidney Exhibiting Unusual Features, Am. J. Surg. **55:** 156, 1942.

A case of pelvic kidney is reported in a 26-year-old female who complained of pain in the right lower quadrant of the abdomen. At operation, a small kidney was found the upper pole of which was incarcerated due to pressure from the encircling large renal vessels. Rotation of the kidney so that the pelvis was displaced forward and the lower pole anteriorly and laterally also resulted. Attempts at freeing the incarceration were unsuccessful due to uncontrollable bleeding, and this necessitated nephrectomy. The author believes that the patient's pain was due to the pull of the renal vessels which also produced compression and rotation of the kidney.

FRANK SPIELMAN.

Labor, Physiology, Management, Complications

Beruti, Josué A.: Birth of the Argentine Quintuplets, Semana méd. 51: 689-697, 1944.

The author has reconstructed the event from the data furnished by the parents, Franco and Ana Diligenti, and by the midwife, Angela Delfino, who attended the birth with the help of her niece. The data obtained must be regarded as reliable because the parents and midwife are intelligent persons who gave clear and precise answers to the questions, without any reserve.

Ana A. de Diligenti, Italian, 35, with normal antecedents, has a son, 14, from a former union and a son, 7, of her present union. Five and a half years ago, she had a triplet abortion of two and a half months.

The last menstruation occurred at the beginning of October, 1942; birth was expected about the middle of July, 1943. The pregnancy was uneventful.

During the morning of July 14, the patient developed slight, irregular pains and was admitted to the residence of the midwife.

At 7 P.M., examination revealed an extremely tense abdomen, many fetal parts, fetal heart tones all over. The diagnosis made at seven months of twin pregnancy was confirmed.

At 9 P.M. the pains disappeared until midnight, during which time the patient slumbered. On July 15, at 1 A.M. there was a slight loss of mucus and blood; contractions reappeared with increasing intensity.

At 7 A.M. the patient went to the bathroom and spontaneous rupture of the membranes occurred. Dilatation was complete. At 8 A.M. a subcutaneous injection of 1 c.c. of pituitrin was given and at 9 A.M. Carlos in vertex presentation was born. At 9:10 A.M. spontaneous rupture of a second sac occurred and the birth of Franco in vertex presentation took place. At 9:25 A.M. Maria Cristina was born as an incomplete breech presentation with manual aid (arms brought down).

At 9:45 A.M. there occurred spontaneous expulsion of a placenta weighing about 700 grams. There was slight loss of blood and the patient felt faint. The midwife wanted to call a physician, but the patient objected strenuously.

At 10:15 A.M. spontaneous rupture of another sac took place with escape of a large quantity of amniotic fluid. Immediate birth of Fernanda in vertex presentation followed. At 11 A.M. there was spontaneous rupture of another sac with the birth of Maria Esther as an incomplete breech presentation with manual aid. The child was markedly asphyxiated but was resusciated by clearing the respiratory tract, cutaneous stimulation, hot bath, artificial respiration, and injection of lobeline.

At 11:15 A.M. there was great loss of blood, controlled by massage of uterus. At 11:25 A.M. there was spontaneous expulsion of a second placenta of about the same volume and weight as the first.

The total loss of blood was estimated at from 800 to 1,000 Gm., and the total amniotic fluid at from 400 to 500 grams.

On the fifth day post partum, the patient was taken home with three of the children. The two weakest ones were left in care of the midwife for four months. The puerperium was normal and afebrile with the exception of the day of the delivery; in the afternoon, the temperature rose to 38 C., but fell to normal in the evening.

After birth, each child was immediately wrapped in cotton wool and kept warm with stove heat and hot-water bags. Incubator, oxygen and carbon dioxide were never used. Baths were forbidden for the first three months.

The weights of the babies after 24 hours were in order of birth: 1,300, 1,200, 1,150, 1,500 and 1,250 grams. From the beginning the babies showed great vitality and had a pink skin without lanugo or vernix caseosa. According to the midwife, they were not premature babies. All are living and well.

J. P. GREENHILL.

Torres, J. I.: Version by Purgation and Enema in Podalic and Transverse Presentations, Rev. de ginec. y d'obst. 3: 115-123, 1943.

The author reports results in 50 cases. Castor oil (30 Gm.) is administered at night, with an enema the following morning. Version was accomplished successfully by this means in 37 cases. In seven, version was not achieved, but was facilitated by purgation and enema. In six instances, this measure failed to produce version.

The author concludes that version by purgation and enema is easy to produce and carries no risk either for mother or fetus. He believes that in every pregnancy of more than seven months, in which there is breech or transverse presentation, this procedure should be used. In case of failure, version by external manipulation should be attempted, taking advantage of the evacuation of the intestines. This can be done without additional preparation of the patient.

J. P. GREENHILL.

Newborn

Paz Silva, Haroldo: Fetal Gigantism at the Maternity Concepcion Palacios, Rev. de ginec. e d'obst. 3: 157-188, 1943.

Accepting 4,500 Gm. as the lowest weight for giant fetuses, the author finds that their incidence in Venezuela is low when compared with other statistics. The highest weight registered at the maternity was 5,100 grams.

The so-called physiologic causes of gigantism were confirmed by the present study, but little can be said about the pathologic causes.

As is usually the case everywhere, the diagnosis of giant fetus was made only at birth and in many cases later. The course of pregnancy was not altered by the presence of a giant fetus. The incidence of breech presentation was 7.69 per cent.

Comparison of the percentage of complications and interventions during labor given by other authors shows that the birth of giant fetuses in Venezuelan women is much less harmful. However, there was a high rate of maternal morbidity which reached 50 per cent.

Taking into consideration the accepted weight of 4,500 Gm., the infant mortality is relatively low, especially when compared with that given by Karl Wilson (20 per cent) and by Zangemeister.

From the results obtained, the authors conclude that spontaneous delivery may be expected in a large percentage of Venezuelan women.

J. P. GREENHILL.

Sorsby, Arnold, and Hoffa, Elizabeth L.: The Sulfonamides in Ophthalmia Neonatorum, Brit. M. J. 4340: 353, 1944.

The authors found that in the treatment of ophthalmia neonatorum, there was no appreciable difference in the action of the four sulfonamides. Sulfapyridine because of its greater toxicity appears to be the least desirable of these sulfonamides. Gonococcal cases responded more rapidly to sulfonamide therapy than did the non-gonococcal cases. The gonococcal cases showed a 51.7 per cent clinical cure within

3 days against 23.2 per cent of the nongonococcal cases. Delay in starting sulfonamide therapy did not affect its efficacy. All cases of corneal ulcer cleared after treatment.

WILLIAM BERMAN.

Pregnancy, Physiology, Diagnosis

Sisco, R. Dominguez, and Agüero, Oscar: Early Signs of Pregnancy Revealed by Genital Examination, Rev. de ginec. e d'obst. 3: 189-197, 1943.

The authors state that the signs found on inspection are those of Jacquemier or Chadwick (cyanosis of the genital mucosas), Kluge (varicosities of the vulva), and Berstine and Montgomery (marked swelling and redness of the orifices of the urethra and Skene's glands).

Digital examination through the vagina or rectum, alone or combined with abdominal palpation, reveals signs belonging to the vagina, cervix, uterine body and adnexa.

The vagina provides the signs of Osiander (increase in the beats of the uterine artery) and Sanger (possibility of feeling the ureters through the posterior vaginal wall).

The cervix gives the signs of Goodall (softening), Sellheim (rounded form of the lower portion) and DeLee (presence of two softened strips parallel to the length of the cervix).

The uterine body, including the isthmus, presents the signs of Hegar (softening of the isthmus giving the impression that the two examining fingers practically touch one another), MacDonald (mobility as if the uterine body and the isthmus were hinged), and Gauss (lateral movement of uterus not transmitted to the cervix).

The difference in consistency between the pregnant and nonpregnant uterus gives the signs of Bonnaire (feeling of ripe fig), Braun-Fernwald (different consistency of the two halves of the uterus), Ladin (above the cervix, a soft spot the size of a small coin which increases gradually as pregnancy advances), Runge (possibility of making a small depression on the anterior surface of the uterus by pressure of the finger through the vaginal wall), and Rasch (peculiar elasticity of the pregnant uterus).

The changes in the form of the uterus have served as a basis for the description of the signs of Piskacek (marked protrusion of one of the horns), Dickinson (marked enlargement of the anteroposterior diameter which becomes greater than the transverse; may be one of the earliest signs), Noble or Noble-Budin (resistance of vaginal cul-de-sacs due to enlargement of lower portion of uterus) and Metzger (bulging of anterior cul-de-sac).

Other signs provided by the uterus are those of Braxton-Hicks (first sign: intermittent contractions beginning from the eighth week of pregnancy; second sign: fetal dance), Bucura (decrease in size by contractions) and Loenne (fluctuation of amniotic fluid).

The adnexa present the sign of Freund and Eupinger (poor mobility and pain on pressure of the ovary which contains the corpus luteum of the pregnancy).

Nowadays many of these signs have only a historical interest and their investigation is doubtful and not without danger in many cases. But it is also true that all means must be used to reach a positive diagnosis without jeopardizing the interests of mother and fetus. The investigation of the signs of Goodall, Noble, Piskacek, Hegar, etc., together with other manifestations outside the genitalia, must lead to the correct diagnosis in most cases; but when there is doubt, and knowledge of the presence of pregnancy is imperative, recourse must be taken to the biologic tests which are about 100 per cent reliable.

J. P. GREENHILL.

Correspondence

Placental Changes in Toxemia of Pregnancy

To the Editor:

It was gratifying to note that in their excellent article Jack H. Hill and Wm. K. Trimble (Placental Infarction as a Diagnostic Criterion of Maternal Toxemia, Am. J. Obst. & Gynec. **48**: 622, Nov., 1944) reported that they could find no placental changes characteristic of so-called toxemias of pregnancy. This is in close accord with our report (Siddall, R. S., and Hartman, F. W.: Infarcts of the Placenta: A Study of Seven Hundred Consecutive Placenta, Am. J. Obst. & Gynec. **12**: 683, Nov., 1926). Examinations of thousands of placentas since our publication has convinced me of the essential correctness of our original observations. Infarction of every kind is likely to be greater with the toxemias (though not necessarily present at all), but in agreement with Hill and Trimble I have been unable to identify certain other placental changes confidently described by some as peculiar to toxemia.

Of interest in another respect was the nearly identical incidence of toxemia in their cases and ours (6.5 and 6.4 per cent), using essentially the same criteria. I strongly suspect, however, that even these comparatively low figures fail to give the true picture. It is to be noted that they are derived from hospital series and therefore presumably include a number of patients who would have been delivered normally elsewhere but were sent to the hospital because of the toxemia. My associate, Dr. Harold C. Mack, and I found that less than 4 per cent of the obstetric patients regularly under our care developed toxemia, and this figure is confirmed by that of 4.4 per cent at Harper Hospital, where there is a very low rate of emergency obstetric admissions (Siddall, R. S., and Mack, H. C.: Weight Changes and Toxemia of Late Pregnancy, Am. J. Obst. & Gynec. **36**: 380, Sept., 1938). The true incidence of toxemia, then, is probably considerably lower than usually estimated on the basis of hospital statistics. This point is important when, for instance, a possible preventive of toxemia is being tried out in consecutive cases. Incidentally, though readily granting the value and advantages of prenatal observation in discovering toxemia early, I am not convinced that any measures so far suggested are efficacious in actually preventing its onset. There are bits of evidence suggesting that some may even be injurious. Possibly to be included in this group is the present popular one of strenuously trying to prevent water retention, since it is to be remembered, for example, that in the hot months when some degree of demonstrable edema is found in nearly every woman late in pregnancy, toxemia is least common. And, one might cite the fact that eclampsia with associated edema is generally less severe than the "dry" type.

Roger S. Siddall, M.D.

Detroit, Mich.
Dec. 14, 1944.

Benefit From Early Clamping of Umbilical Arteries

To the Editor:

In any part of the body from which the arterial blood flow has been completely interrupted further, movement of venous blood is dependent upon negative pressure. A compression or milking of that area rapidly produces empty veins

and a bloodless area. It has been my belief that the application of this knowledge in the treatment of the umbilical cord should result beneficially to the newborn infant.

Recent literature has emphasized the importance of delayed clamping of the cord,[1, 2] one writer's work suggesting that there is even an increase in the infant's blood volume during the period of placental expulsion.[2]

During the past several months I have been attempting to improve on the above-mentioned method of delayed clamping of the cord by an immediate clamping of the umbilical arteries, followed by gentle stripping of the umbilical vein. This procedure disrupts the blood supply to the placenta and results in an exsanguination into the body of the infant, there occurring a conservation of blood which otherwise would remain in the placenta or be spilled, if one practices the method of bleeding the placenta in order to facilitate its separation and expulsion.

I have frequently observed that in cases of asphyxia administration of oxygen to the mother improves the color of the infant. For this reason I have not clamped the umbilical arteries until the newborn infant cries. However, my observation may be erroneous, as excellent recent work seems to prove the immediate separation of the placenta in all normal cases, with rare exceptions. This being true, such an early disconnection with the maternal oxygen source would make unnecessary any hesitation in clamping of the arteries.

Observation has convinced me of the rapid depletion of blood in the umbilical vein and placenta. On many occasions I have compressed the placenta, after its delivery, and milked its surface veins with noticeable increased diminution in the amount of contained blood. I believe I have seen the infants' color improve.

In most cases the umbilical arteries are easy to define and clamp. In large cords a single blade of the hemostat is made to pierce the cord adjacent to the vein, and all tissues except the vein are clamped.

My observations have been such as to make insecure any conclusions I have drawn. This small contribution is offered in the hope that it might interest someone whose volume of work and access to proper facilities for measurements justifies a conclusion on this method of handling the cord.

G. M. A. Fortier, M.D.

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1. Titus, Paul: The Management of Obstetric Difficulties, St. Louis, 1940, The C. V. Mosby Co., ed. 2, p. 850.
2. Serbin, W. B.: S. Clin. North America **23**: 73-83, 1943.
3. O'Conner, Cornelius T.: Am. J. Obst. & Gynec. **48**: 683, 1944.

Little Falls, Minn.
Dec. 18, 1944.

Items

Melbourne W. Boynton, M.D., A War Casualty

Colonel Boynton, of Chicago, instructor in obstetrics and gynecology at the Lying-In Hospital, a diplomat of the American Board of Obstetrics and Gynecology, was killed Aug. 19, 1944, as the result of an experimental parachute jump which was to record the effects of a free fall of 35,000 feet. Interested in aviation, he was rapidly advanced in rank and became head of the medical division of the Office of Flying Safety in the Army Air Services. Dr. Boynton was a member of the Chicago Gynecological Society.

American Board of Obstetrics and Gynecology

Examinations

All candidates will be required to take both the Part I examination and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

Notice of the exact time of the Part II examination will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations as they apply to civilian candidates.

Applications for the 1945 examinations are now closed.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

Necrology

FRANK WORTHINGTON LYNCH, M.D., obstetrician and gynecologist of San Francisco, Calif., died Jan. 12, 1945, of a heart attack at the age of 73 years. Dr. Lynch was born in Cleveland, Ohio, 1871, a graduate of Johns Hopkins, 1899, where he then served as resident, instructor, and associated obstetrician before settling in California. He became Professor of Obstetrics and Gynecology at the California University and after his retirement was made an Emeritus. He was a Diplomat of the American Board, a former President of the American Gynecological Society and the Pacific Coast Society of Obstetricians and Gynecologists, and member of several leading specialist societies as well as a Governor of the American College of Surgeons. Dr. Lynch was the author and co-author of various medical works, a frequent contributor to the literature, and a member of the Advisory Editorial Board of the JOURNAL since its inception.

WALTER PONDER CONAWAY, A.B., M.D., Senior Attending Gynecologist at the Atlantic City Hospital, died at his home after a long illness Jan. 12, 1945. Born in Leipzig, Del., in 1871, graduated in Medicine at the University of Pennsylvania, a member of many professional societies, he was president of the Medical Society of the State of New Jersey in 1927, a Fellow of the American College of Surgeons, and a Diplomat of the American Board.